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Editorial

Atherosclerosis and the Nature of the Arterial Wall

ATHEROSCLEROSIS and its consequences are of such frequent occurrence and of such devastating implications that it would be an understatement to say that these constitute our leading health problem. Without review of the statistics with which we are all familiar, the bald fact is that the adult has, in a manner of speech, a choice of meeting his end either by way of cancer or of some complication of atherosclerosis. If about two out of 10 experience cancer, six or seven out of 10 will suffer the sequelae of atherosclerosis.

How does one approach study of a disease such as atherosclerosis? Perhaps because we are heady with the wine of success in dealing with infectious diseases and vitamin deficiencies, which stem from single causative agents, most of us have focused on the likelihood that atherosclerosis is due to a disturbance in cholesterol metabolism or a dietary impropriety. None of the discussion I am about to offer is intended to negate the involvement of these factors in spontaneous atherosclerosis, for it is quite clear that cholesterol does accumulate in the intima of arteries, that hypercholesteremia frequently is positively correlated with severity of atherosclerosis, and similarly that diet conditions, at least in some situations, the severity of atherosclerosis. Certainly, cholesterol in some form is a factor in atherosclerosis. But it may be well to be reminded that so is the arterial wall.

My contention has been and continues to be that the receptivity of the arterial wall to cholesterol is a major factor in the genesis of atherosclerosis.[1] In this connection one quite properly may ask: Why is it that the pulmonary artery is virtually immune to atherosclerosis? Why is syphilitic aortitis, a disease characterized by scarification of the arterial wall, accompanied by remarkably severe atherosclerosis? Why are the lesions of atherosclerosis typically of a focal nature? None of these questions has clear answers now but we do know that the pulmonary artery does not undergo a breakdown and calcification of the elastic tissue in its wall that most other arteries do,[2] we do know that syphilitic aortitis is accompanied by breakdown of the elastic lamellae of the media and replacement of them by white fibrous connective tissue, and we do know that the sites of predeliction for atheromata are also the sites at which stress occurs (such as arterial bifurcations) and that at these sites the breakdown of the elastic tissue is more severe than elsewhere.[3, 4]

My laboratory has over the years accumulated considerable data, as have others before us, indicating that, beginning with the end of the second decade of life and becoming progressively more severe with the passage of time, there is a typical pattern of alteration

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in the elastic elements of the wall of human arteries.[5] In both muscular and elastic arteries the plates of elastic tissue, barriers to free movement of materials between the intima and media except for the widely spaced fenestrations, begin to fray, fragment, and calcify. This process continues throughout adulthood until there is little or no trace left of the original elastic lamellae. All that remains are masses of calcified fragments or granules of elastic tissue.[3-6]

This process of elastic tissue deterioration does not occur in the pulmonary artery just as atheromata do not form in this vessel.[2] In pulmonary hypertension, however, one does find elastocalcinosis and one also finds atheromatosis. We have made the point, as yet not accepted, that the breakdown of the elastic lamellae precedes and is requisite to formation of atheromata. The implication is that receptivity of the intima of arteries to cholesterol accumulation is conditioned by the integrity of the elastic lamellae.

Perhaps it will be worth while to take a broader view of the whole problem: Why do chronic diseases including atherosclerosis occur at all? The essential features of Darwinian evolution include (1) development of individual variations, (2) struggle for existence, and (3) survival of the fittest. Thus, a mutation or variation of an unfavorable type that expresses itself early in life will unsuccessfully compete for existence and fail to perpetuate itself. But what happens in a species that experiences senescence? There is a gradual decrease in reproduction vigor and finally a termination of breeding. The unfavorable mutation appearing prior to or early in reproductive life will tend to be eliminated from the species by natural selection. But an unfavorable mutation expressing itself predominantly late in or after reproductive life cannot possibly be eliminated from the species. On the contrary, it is inevitable that the longer the species survives, the greater will be the number of unfavorable mutations that will accumulate in the species. If, indeed, there is a genetic basis to the chronic diseases in the human population as there appears to be, this may be the biological basis for their existence. To put it another way, once senescence, or a marked decrease in reproductive vigor, appears in a species it is virtually inevitable that genetically based chronic diseases will appear in that species.

Atherosclerosis as a specific example of the chronic diseases may well fall in this category of unfavorable mutations immune to the purging action of natural selection. Spontaneous atherosclerosis, despite popular impressions, is not a new disease. On the basis of study of Egyptian mummies dating as far back as 1500 B.C., Ruffer[7] established that atherosclerosis as we know it today not only existed then but also occurred very frequently. This despite the fact that dietary and other exogenous factors were very different 3,500 years ago from what they are today.

Still further, atherosclerosis cannot be considered to be restricted to the human population. Spontaneous atherosclerosis occurs very widely throughout the mammals, carnivorous and herbivorous, in and out of captivity. The studies of Fox[8] have shown that one can list most of the genera of the mammals as victims of spontaneous atherosclerosis. From a phylogenic viewpoint, atherosclerosis is not only older than man[9] but is also older than the class Mammalia. The class, Aves, is replete with specific instances of occurrence of spontaneous atherosclerosis. As Paterson has shown,[10] spontaneous atherosclerosis in the chicken is indistinguishable from that which occurs in the human. Where did the mutation of susceptibility to atherosclerosis appear? The existing literature and current studies seem to indicate that the disease does not occur in the fishes, and I have not been able to find any record of atherosclerosis in the Amphibia. Gross and histologic analysis of a limited number of reptiles indicate, as a first approximation, that at least in modern reptiles atherosclerosis does not occur. Yet birds and mammals, both of which suffer atherosclerosis, have a common ancestry in the Reptilia. It would seem that one might search in this common ancestry for the appearance of a change in the structure, chemistry, or physi-

ology of the circulating system that may be correlated with susceptibility to atherosclerosis. It is interesting to note, for example, that reptiles possess two aortic arches while birds and mammals possess but one. It is also interesting to note that arterial pressures in Amphibia and reptiles are approximately one half that of birds and mammals. Nothing is known of the fate of arterial elastic lamellae with age in reptiles, a study that might be very informative. Whatever the type of study may be, it is entirely possible that analysis of arteries prior and subsequent to the phylogenetic appearance of atherosclerosis may give us valuable clues applicable to understanding of and ultimate control of human atherosclerosis.

ALBERT I. LANSING

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The Early History of Instrumental Precision in Medicine

Even those among you given to reading the authors of the end of the last and the first twenty years of the present century, may be surprised to learn that statements of the numbers of pulse and respiration are very rare in Rush, Cullen and their contemporaries. Heberden and Falconer who, perhaps, set too much value on pulse counts, made no impression on their contemporaries. In Corvisart on the Heart we hear little or nothing in this direction, and in seven hundred pages of Laennec there is one pulse count and no numeration of the breathing. It seems incredible; but not until the later French school developed its force do we find in reports of cases the beginnings of those systemic numerations of the breath and pulse which are met with in modern cases. . . . It was not until a later day, and under the influence of the great Dublin school, that the familiar figure of the doctor, watch in hand, came to be commonplace.—S. WEIR MITCHELL, M.D., *Transactions of the Congress of American Physicians and Surgeons,* Second Triennial Session held at Washington, D.C., 1891. New Haven, The Congress, 1892, p. 179.

Hypertension Secondary to Renal Artery Occlusive Disease

By Dorothee Perloff, M.D., Maurice Sokolow, M.D., Edwin J. Wylie, M.D., Donald R. Smith, M.D., and Alphonse J. Palubinskas, M.D.

THE PROLONGED disability and shortened life span of patients with hypertension, as well as the expense and inconvenience of lifelong drug therapy, emphasize the urgent need for detecting curable forms of hypertension.

The concept of an intimate causal relationship between hypertension and renal disease has developed slowly over the past 125 years. Bright, in 1836, noted the association of cardiac enlargement and chronic renal disease,[1] while Mahomed postulated in 1881 that high arterial pressure was a cause of Bright's disease.[2] The first to report the onset of hypertension in a patient with unilateral pyelonephritis resulting from a ureteral stricture and the disappearance of the hypertension after nephrectomy was Crabtree (1927).[3] After Ask-Upmark's detailed description of six cases of juvenile malignant hypertension in which congenital unilateral renal abnormalities were found at autopsy (1929),[4] Butler recorded in 1937 for the first time the successful treatment of hypertension by nephrectomy in a child with unilateral pyelonephritis.[5] A similar but unreported case was observed by Kerr in 1936.[6] In the same period of time Goldblatt and his co-workers (1934) investigated extensively the experimental production and mechanism of hypertension in animals in which the renal arteries had been ligated,[7] and several authors subsequently amplified the studies of the causal relationship between renal ischemia and hypertension.[8-12] The influence of these experimental studies on clinical thinking became evident in four papers that appeared in 1938 dealing with the association of hypertension and occlusive renal artery lesions[13, 14] and with the cure of the hypertensive disease due to unilateral renal artery occlusion by nephrectomy.[15, 16] Numerous subsequent reports on the therapeutic effect of nephrectomy followed until Smith, in 1948 and again in 1956,[17, 18] and Perera and Haelig, in 1952,[19] critically reviewed the literature and concluded that only about one fifth of the patients who had had a nephrectomy were cured of their hypertension. However, in arriving at this conclusion, no distinction was made between patients with parenchymal renal disease and those with occlusion of the renal artery, and no allowance was made for the clinical improvement in those patients who did not become entirely normotensive.

The observation in animals by Wilson and Byrom,[20] that the kidney distal to a stenotic renal artery was "protected" from the vascular lesions of malignant hypertension, was confirmed in man by Bauer and Forbes (1952)[21] and Laforet (1953).[22] These authors stressed that the kidney on the side of the arterial occlusion was potentially the healthier one and, if possible, should be preserved.

A successful endarterectomy of a partially occluded renal artery with restoration of the circulation in the ischemic kidney and cure of hypertension was reported for the first time by Freeman et al. in 1954.[23] The importance of aortography for the detection of renal artery lesions was emphasized in 1956 by Poutasse[24] who, together with Dustan, reported in 1957 30 cases with renal artery disease found among 104 selected hypertensive patients examined by aortography over a 2-year period.[25] In a more recent paper, Poutasse described his experience with over 300 hyper-

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Table 1

*Indications Used for the Selection of Hypertensive Patients for Renal Arteriography**

Clinical history
Recent onset or documentation of hypertension (within 2 years)
Recent increase in the severity of existing hypertension
Onset of hypertension in patients under 20 or over 50 years of age
Negative family history of hypertension
Recent flank pain or trauma to the flank
Physical examination
Papilledema or hemorrhages and soft exudates in the fundi (malignant hypertension)
Epigastric or flank bruit
Evidence of vascular insufficiency of the extremities or aortic aneurysm
Radiologic and laboratory studies
Disparity in renal size or function on intravenous pyelogram, or abnormal renal calyceal pattern
Unequal renal sodium and water excretion by differential retrograde study

*The absence of any or all of these indications was not considered a contraindication to arteriography in patients with severe hypertension.

tensive patients, 26 per cent of whom were found to have occlusive renal artery lesions.[26] The blood pressure fell in 80 per cent of those who survived after corrective surgery. DeCamp and Birchall,[27] Feste et al.[28] and Brown et al.[29] have published similar experiences.

In the past 8 years, the relationship of hypertension and renal artery obstruction has been the object of intensive clinical study at the University of California Medical Center. By the use of arteriography, altogether 70 hypertensive patients have been found to have renal artery abnormalities; 66 of these were diagnosed in the past 3 years. This high number suggests that renal artery obstruction is a relatively common finding and potential cause of secondary hypertension. The present study was undertaken to develop a reliable method to differentiate patients with renal artery abnormalities from the hypertensive population at large and to determine the value of renal vascular surgery for the treatment of this type of secondary hypertension.

Materials and Methods

A total of 110 patients with sustained hypertension (blood pressure above 150/90 mm. Hg) underwent renal arteriography between November 1952 and November 1960. All patients were personally seen and examined by the authers. In all but nine cases the radiographic studies were made in the past 3 years. The possibility of renal artery occlusion was considered in the evaluation of every hypertensive patient and arteriography was performed when one or more of the indications listed in table 1 were present. In a few cases the presence of sustained severe hypertension was considered an indication for arteriography.

Indications for Arteriography

The indications for arteriography proposed by Poutasse and Dustan[25] have been listed in table 1 with slight modifications. They require some explanation and amplification.

Recent or sudden onset of hypertension is difficult to establish unless recent normal blood pressure readings, immediately preceding the onset of the hypertension, are available. In many patients with apparently recent onset of hypertension, previous insurance, military, blood bank, industrial, or maternity examinations reveal borderline or slightly elevated readings suggesting that the hypertension is of longer duration. The presence of arteriovenous compression in the ocular fundi may also suggest that the hypertension is not of recent origin.

Equally difficult to verify is a *recent increase in hypertension.* A single or even several unusually high readings may be mistaken for an increase in the degree of existing hypertension, whereas they may only reflect the lability of the blood pressure due to emotional factors, confusion about medication, or unknown transient causes. A review of past blood pressures may reveal similar transient rises. A definite change

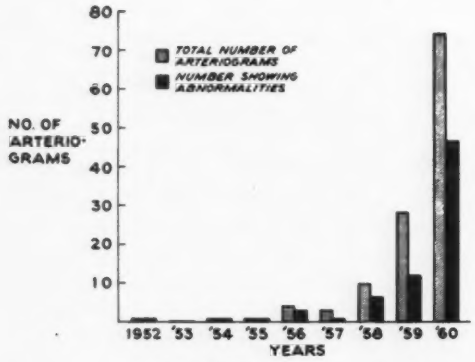

Figure 1

The yearly distribution of renal arteriograms performed at the University of California Medical Center (November 1952 to November 1960) and the number of renal artery abnormalities found.

in the range of the blood pressure in a given patient is, therefore, difficult to document unless weekly averages of several daily blood pressure readings are available. Since in most patients the blood pressures are recorded irregularly and under variable casual conditions, such serial readings usually are not available.

Essential or primary hypertension often occurs in several generations or members of one family and usually manifests itself first between the ages of 20 and 50 years.[30] An isolated case of hypertension in the *absence of a familial history* as well as hypertension appearing in a patient *under 20 or over 50* is therefore more likely to represent a case of secondary hypertension requiring search for a primary cause. However, an accurate family history is notoriously difficult to obtain because of lack of accurate information. Persistent, careful, detailed questioning and objective documentation of the blood pressure in relatives are often necessary before the absence of a family history of hypertension can be taken for granted.

A history of recent, unexplained, sudden *flank pain or of trauma* to the flank may be associated with a renal vascular accident, thrombosis, or hemorrhage, and should be elicited if present.

Malignant hypertension was considered established, in this study, when papilledema was observed in a hypertensive patient, with or without renal impairment. In a few cases the sudden development of hemorrhages and soft exudates in the ocular fundi was considered sufficient evidence of impending malignant hypertension to warrant arteriography.

Detection of an *epigastric or flank bruit* requires careful attention. It may be heard only in a very localized area of the epigastrium or flank; it may be intermittent. The bruit may be so faint that it can be heard only in a quiet room or in the absence of loud bowel sounds, and may easily be missed in a noisy ward or office. It is usually louder when the patient has tachycardia, when the blood pressure is higher than usual, or when the cardiac output is elevated, as with effort or exercise. The bruit may be high-pitched and easily heard with the diaphragm attachment or so low-pitched that it can be heard only with a bell attachment of the stethoscope. It is, of course, important to distinguish an abdominal bruit from a systolic murmur transmitted from the heart or a bruit transmitted from the femoral vessels.

Table 2

*Classification of Arteriographic Abnormalities in 70 Patients**

Significant abnormalities	54
Unilateral renal artery occlusive disease	19
Atherosclerotic (14)	
Fibromuscular hyperplasia (5)	
Bilateral renal artery occlusive disease	31
Atherosclerotic (20)	
Fibromuscular hyperplasia (10)	
Embolic (1)	
Unilateral hypoplasia of the kidney and renal artery	4
Minor abnormalities	16

*110 patients were studied between 1952-1960; 39 arteriograms did not show renal abnormalities and one study was unsatisfactory for definite diagnosis.

The presence of a renal artery obstruction was considered a likely possibility in hypertensive patients with clinical evidence of *atherosclerosis obliterans* or aneurysm of the aorta or iliac or femoral vessels. Atherosclerosis obliterans was considered present when a history of peripheral vascular insufficiency was confirmed by the finding of diminished or absent pulses, with or without bruits, in the lower extremities, or the finding of localized enlargement of the abdominal aorta consistent with an aneurysm detected either by palpation or radiologically. Calcification of the pelvic vessels or arch of the aorta was not in itself considered an indication for aortography, nor was a history of cerebral or coronary artery disease.

Disparity in the size of the two kidneys, especially in the absence of the calyceal abnormalities of chronic pyelonephritis has been used as an indication of unilateral renal atrophy secondary to renal ischemia. Actual renal size may be diffi-

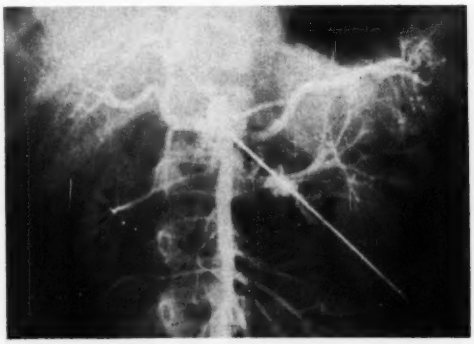

Figure 2

Renal arteriogram of an 11-year-old girl; small right kidney and right renal artery with compensatory hypertrophy of the left kidney. Left renal artery obscured by overlying needle and calcified mesenteric lymph nodes.

cult to evaluate because of rotation of one kidney, overlying bowel shadows, or lack of clear definition of the entire renal shadow. In determining the size of the kidneys by intravenous pyelography, the longitudinal diameter of each was measured to the nearest 0.1 cm. The width of the renal shadows was not measured unless a marked disparity was noted, in which case the kidneys were compared by mass rather than by length. A difference of 1 cm. or more in length was considered significant, since normal variation in size has been reported as ± 0.5 cm. with the left kidney usually being the larger.[31] Differential renal function as determined by pyelography, unless grossly impaired on one side, was evaluated by the promptness of the appearance and the density of the radiopaque dye on the 1-, 3- and 5-minute films after a standardized rapid injection. A normal pyelogram was not considered a contraindication to arteriography.

Technics

Aortography was generally performed by the standard translumbar route under local or general anesthesia. In 10 patients, retrograde renal arteriograms were obtained by the Seldinger technic.[32] Intravenous arteriography was not attempted because this technic often does not give sufficiently detailed visualization of the renal arteries.

Differential renal function studies were performed in 61 patients by various modifications of the retrograde technic described by Howard et al. and Connor et al.[33, 34] Diuretic medication was discontinued before the test, and adequate sodium excretion was assured by allowing patients a normal dietary sodium intake, occasionally with additional oral salt, the day before urologic study. Whenever possible, the test was performed with a retrograde catheter in place in each renal pelvis. However, when excessive leakage occurred around the ureteral catheters, a bulb ureteral catheter was inserted in one side while the urine from the other kidney was collected directly from the bladder. Most patients were orally hydrated before the test but occasionally glucose and water was administered intravenously during the period of urine collection. Timed urine specimens were analyzed for volume, and phenolsulfonphthalein, sodium, and chloride excretion. In many instances potassium content and total osmolarity were also measured. A 50-per cent difference in water excretion and a 20-per cent difference in sodium were considered significant, and the results from the test were referred to as positive.

Table 3

Comparison of the Clinical Characteristics of Patients with Localized Occlusive Renal Artery Disease of Different Etiologies

	Atherosclerotic	Fibromuscular
Number of patients	34	15
Sex: Men	21	0
Women	13	15
Duration of hypertension:		
Less than 1 year	9	5
1-5 years	7	3
Greater than 5 years	17	7
Age, mean (range)	53 (36-72)	38 (17-49)
Under 45	7 (21%)	13 (87%)
Over 45	27 (79%)	2 (13%)
Negative family history of hypertension	11	5
Hypertensive severity		
Mild	11	1
Severe	23	14
Hemorrhages, soft exudates or papilledema in the fundi	14	1
Impaired total renal function	9	0
Recent onset or increase in severity of hypertension	14	8
Location of arterial stenosis		
Unilateral	15	5
Bilateral	19	10

Results

The number of renal arteriograms done in our hospital in the past 8 years (November

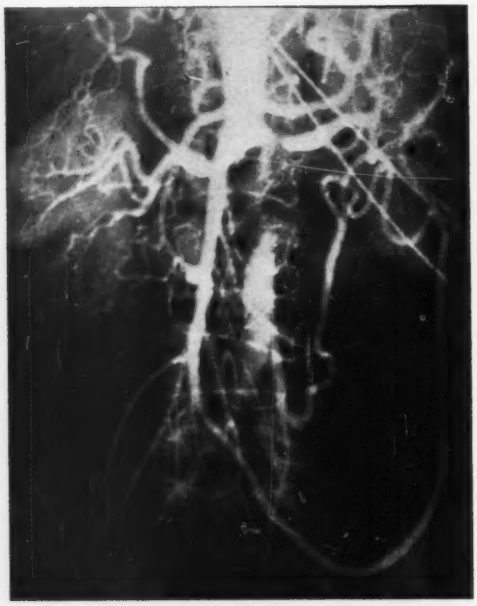

Figure 3A

Aortogram of a 46-year-old woman; complete obstruction of the abdominal aorta and stenosis of the proximal portion of the left renal artery, found at operation to be due to atherosclerosis.

Figure 3B

Aortogram of a 63-year-old woman; demonstrating bilateral proximal renal artery stenosis due to atherosclerosis.

1952 to November 1960), as well as the number of patients found to have abnormalities, are shown in figure 1. During the 8-year period, 122 arteriograms were performed on 110 patients. The increasing awareness and suspicion of renal artery abnormality in hypertensive patients is reflected in the yearly increase in the number of studies; more than 60 per cent were done within the past year.

Radiologic Findings

Abnormalities of the renal artery were demonstrated in 70 of the 110 patients (table 2). In 54 the abnormalities were judged to represent significant occlusive disease, on the basis of previous experience with visualization of major vessels such as the carotid, femoral, or popliteal arteries confirmed at operation. The occlusive renal artery disease in these 54 was thought to represent sufficient obstruction to renal blood flow to be a potential cause of renal ischemia and subsequent hypertension. In 16 patients the abnormalities were considered minor, including an isolated aneurysm, mild intimal irregularities, or tapering of either or both arteries. The causal relationship of these lesions to the hypertension appeared unlikely and surgical exploration and reconstruction were not advised. These patients are being observed, however, and serial studies are planned. A small kidney and artery on one side with a normal or hypertrophied opposite kidney were detected in four patients. In 39 patients no renal artery abnormalities were found. The arteriographic study was not considered adequate in one patient (a child) but was not repeated because the patient's blood pressure subsequently returned to normal levels without therapy.

In addition to the picture of a small kidney with a uniformly narrowed renal artery (fig. 2), two distinct radiologic patterns were differentiated in patients with stenotic renal arteries. The characteristic arteriosclerotic lesion located at the origin or proximal third of the renal artery (fig. 3) was found in 34 patients, unilaterally in 14 and bilaterally in 20 (two of these had an associated aortic aneurysm). This radiologic picture was found, at surgery, to represent a plaque at the renal artery orifice or origin from the aorta, extending concentrically around or projecting irregularly into the lumen of the artery. The second type of radiologic abnormality (fig. 4) occurred in the middle and distal thirds of the

renal artery, occasionally extending into the intrarenal branches, and consisted of alternating areas of constriction and dilatation of the arterial lumen, often associated with small aneurysms. This lesion was diagnosed as fibromuscular hyperplasia of the media on pathologic examination in the nine patients who were operated on and in whom a pathologic specimen was available, and it was assumed that the same process was involved in the others with a similar radiologic pattern who were not explored. Five of these patients have been previously reported and the radiologic patterns have been described in all of these 15.[35, 36] In one patient, both types of radiologic abnormality were diagnosed radiologically.

Clinical Picture of Patients with Major Renal Artery Abnormalities

The group of patients with radiologic abnormalities believed to be due to atherosclerotic lesions and the group with a radiologic pattern of fibromuscular hyperplasia differed in several respects (table 3, fig. 5). The atherosclerotic lesions occurred in both men and women of the older age group, while fibromuscular hyperplasia was seen in relatively young women. More than 50 per cent of the atherosclerotic group were in classes III and IV hypertensive severity—based on the level of the resting blood pressure, degree of cardiac enlargement, fundal abnormality, and electrocardiographic evidence of left ventricular hypertrophy;[37] 20 per cent of these had papilledema. On the other hand, all but two of the group with fibromuscular hyperplasia were in class I or II hypertensive severity and none had papilledema. Total renal function, as measured by the creatinine clearance, nonprotein nitrogen, and the phenolsulfonphthalein excretion was normal in all of the patients with fibromuscular hyperplasia but impaired in nine of those with atherosclerosis.

Complications from Arteriography

The complications observed following the 112 translumbar arteriograms fell into the following categories: (1) those related to general anesthesia, including transient hypotension (eight cases), nausea and vomiting (13 cases), and hoarseness from intubation (two cases); (2) circulatory derangements secondary to the aortic puncture, including reflex hypotension (three cases), retroperitoneal bleeding (14 cases), hematuria (11 cases), and transient decrease in renal excretory function (24 cases); (3) miscellaneous problems, including local lumbar tenderness or swelling (30 cases), allergic reaction to the opaque medium (one case), thrombophlebitis (two cases), and an acute case of pancreatitis. No deaths occurred, but one patient had cardiac arrest while under general anesthesia and required prolonged hospitalization for pleural effusion, bleeding, and infection resulting from the emergency thoracotomy. Two patients who presumably had retroperitoneal bleeding were given transfusions and one patient required vasopressor therapy for sustained hypotension. Following the routine use of local anesthesia the problems in the first category have no longer occurred.

Among the 10 patients examined by the retrograde femoral technic (Seldinger), only one minor complication occurred: a local hematoma with pain and paresthesias lasting several days.

Validity of the Indications for Arteriography

All the indications for arteriography listed in table 1 were not present in every one of the patients in whom abnormalities were demonstrated, nor were any of the indications consistently absent in the patients in whom abnormalities were not found. In order to determine which indications were most often present in patients with renal artery abnormalities, we have compared three groups of patients (table 4), namely those with (1) significant renal artery abnormalities, (2) those with minor irregularities, and (3) those in whom no lesion could be detected. In addition, the distribution of the three groups of patients among the four classes of hypertensive severity previously mentioned was compared.

Of the 54 patients in group I, only three manifested a single indication for study; in all the others, two or more indications were present. On the other hand, a single indica-

Table 4

Relationship of the Indications for Arteriography and Severity of the Hypertension to the Presence of Radiologic Abnormalities of the Renal Artery

	Total patients in whom indication was present	Group I, significant lesion (54)	Group II, minor lesion (16)	Group III, normal renal arteries (39)
Clinical history				
Recent onset or documentation of hypertension	41	25	0	16
Recent increase in the severity of existing hypertension	24	12	7	5
Onset of hypertension in patients under 20 years	18	8	3	7
over 50 years	22	15	2	5
Negative family history of hypertension	36	17	6	13
Recent flank pain or trauma to the flank	4	4	0	0
Physical examination				
Malignant hypertension (papilledema)	11	8	1	2
Hemorrhages and exudates in the fundi	10	7	1	2
Epigastric or flank bruit	62	42	11	9
Atherosclerosis obliterans of the aorta or extremities	38	27	4	7
Laboratory, radiologic				
Disparity in renal size or function by pyelography	40	23	2	15
Unequal renal sodium and water excretion (Howard test)	15	14	0	1
Overall hypertensive severity*				
Class I	17	6	1	10
Class II	43	21	9	13
Class III	36	18	4	14
Class IV	13	9	2	2

*Hypertensive severity classified according to the level of the resting blood pressure and degree of fundal, cardiac, and renal impairment resulting from the hypertension.

tion for arteriography was present in eight of the 39 patients without a lesion. The likelihood of finding a lesion appears greater in patients with multiple indications than with only one indication.

Recent onset or documentation of hypertension or recent increase was recorded in 68 per cent of patients in group I (those with lesions) and in 54 per cent of those in group III (those without lesions). The absence of a family history and the percentage of patients with onset of hypertension before age 20 or after age 50 did not differ grossly among the three groups.

A bruit was heard in 62 patients, 53 of whom had a demonstrable abnormality, although 11 of these were minor. Of the 48 individuals without a bruit, an occlusive lesion was detected in 12. A bruit, thus, was associated with a lesion in a large percentage of cases, but the absence of a bruit did not preclude renal artery abnormalities. In eight of 11 patients with papilledema, and in seven of 10 with hemorrhages and exudates in the fundi, arteriography demonstrated a stenotic process in one or both renal arteries. Clinically apparent atherosclerosis obliterans in the aorta and iliac vessels was associated with renal artery abnormalities in over 80 per cent of the cases. Disparity in renal size or function was found equally in patients with and without lesions. On the other hand, 17 per cent of the patients with major lesions had normal intravenous pyelograms.

Differential renal function studies (Howard study) resulted in a significant difference (positive test) in 15 patients, 14 of whom were found to have an arterial lesion, six of which were bilateral. The other patient had unilateral chronic pyelonephritis without arterial abnormality. No significant difference in renal function (negative test) was observed

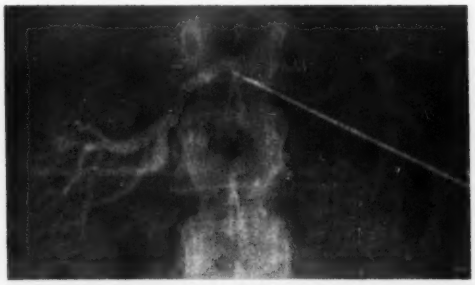

Figure 4A

Right renal arteriogram of a 38-year-old woman; presenting localized stenosis and poststenotic dilatation of the middle and distal thirds of the renal artery due to fibromuscular hyperplasia.

Figure 4B

Aortogram of a 49-year-old woman; bilateral multiple areas of stenosis and dilatation of the distal renal artery typical of fibromuscular hyperplasia.

in 46 patients; 13 with unilateral lesions, eight with bilateral lesions, and 25 without arterial abnormalities.

Several combinations of indications were associated with a high percentage of lesions. In 86 per cent of patients with the combination of a bruit and recent onset of hypertension, and in 100 per cent of those with a bruit, clinical atherosclerosis obliterans and disparity in renal size, arteriography demonstrated a significant renal artery lesion.

Operative Findings and Procedures

Of the 70 patients with radiologically demonstrable abnormalities, 40 underwent operation. In one older patient an inoperable aortic aneurysm involving both renal arteries was encountered, and in another case evidence of retroperitoneal infection (residual from a previous procedure) was considered a contraindication to proceeding with a vascular repair.

The decision to perform a vascular repair after preliminary exploration was based on the palpatory finding of a diminished pulse distal to the occlusion, a palpable thrill over the stenotic portion of the artery, the presence of a poststenotic aneurysmal deformity and of a well-circumscribed plaque or area of concentric thickening in the arterial wall. Nephrectomy was performed when the kidney on one side was grossly atrophic, or when the arterial abnormality on one side extended too far into the renal artery branches to permit resection and reanastomosis. Pressure gradients across stenotic segments and flow meter studies were recorded in only a few instances.

In general, the abnormalities found at the operating table in the 38 patients on whom arteriotomy was performed, agreed closely with the radiologic findings, with the following exceptions. In five cases arteriography suggested a bilateral lesion, but at exploration only one side was found to be sufficiently stenotic to require surgical repair. In one patient no abnormality was found at initial arteriotomy, although the radiologic picture suggested bilateral fibromuscular hyperplasia. Two and a half years later this same patient (P.A., table 6) was again studied because of a sudden increase in her hypertension. On the second arteriogram the left renal artery was found to be completely occluded, and the left kidney was much smaller than on the previous examination. The left kidney was removed; it weighed 30 Gm. and showed multiple old infarcts. A stenotic segment in the middle third of the renal artery was palpated by the surgeon but could not be resected for pathologic study. It is unclear whether this patient developed a new lesion or whether a small lesion, which was not palpated at operation earlier, progressed to complete occlusion. Subsequent experience has indicated that the

Table 5

Corrective Surgical Procedures in 38 Patients

	No. of patients	
Endarterectomy of the renal artery		20
Unilateral		13
Uncomplicated	8	
Extensive — including aorta, iliac arteries, mesenteric artery, celiac axis with or without arterial graft (subsequent nephrectomy in 1 patient)	3	
Associated nephrectomy on opposite side	2	
Bilateral		7
Uncomplicated	5	
Associated aortic aneurysm repair	1	
Associated aortic thromboendarterectomy with aortofemoral bypass graft	1	
Splenorenal arterial anastomosis		4
Subsequent nephrectomy of opposite kidney	1	
Segmental resection with end-to-end reanastomosis of the renal artery		6
Unilateral	5	
Bilateral—with subsequent nephrectomy	1	
Nephrectomy—uncomplicated		8
Renal biopsy		14

presence and extent of the occlusive lesion of fibromuscular hyperplasia may be difficult to detect by palpation at the time of operation.

Not all of the patients in whom the arteriographic examination indicated a significant occlusive lesion were submitted to operation. Two patients died before they could be medically prepared for operation; at autopsy, arteriosclerotic plaques at the aortic orifice of the renal arteries diagnosed radiologically were confirmed in both. The arteriographic findings in 12 patients have not yet been confirmed anatomically, either because operation has been refused (three cases), or because the lesion appeared inoperable in view of the extensive bilateral abnormalities extending into the branches of the renal artery (eight cases) or the patient's clinical status would not permit a major surgical procedure, and in one of the 13, operation is still under consideration.

Two of the patients with no demonstrable renal artery lesion underwent nephrectomy for unilateral pyelonephritis and adenocarcinoma of the kidney, respectively. In neither case was the entire renal artery exposed, but no constricting lesion was found in the examined specimen.

The operative procedures and the number of each performed are listed in table 5. In addition to the patient (P.A.) mentioned above, three others had a subsequent nephrectomy—two because of recurrent stenosis on the operated side, and in one patient a nephrectomy was performed on the inoperable right side after the initial shunt procedure on the left proved successful.

Since the majority of the patients were diagnosed and operated on within the past 3 years, the duration of follow-up in most is too short to permit a definite conclusion either that hypertension has been cured or that surgical therapy has failed. The early results, however, are of interest and are tabulated (table 6).

Of the 38 patients who underwent corrective procedures, 31 survived and, of these, 25 (80 per cent) were found to have a sustained postoperative reduction in blood pressure. Of these, 14 patients, with an average age of 34 years, have remained at normal blood pressure levels for a mean period of 11 months (range: 2 months to 7 years), while 11 patients with an average age of 50 years have had a sustained decrease in pressure but not quite to normal levels after a mean of 9 months (range: 2 months to 6 years). The duration of hypertension in all but three of the former group was 2½ years or less, although in two patients it was 8 and 9 years, respectively. On the other hand, among patients whose blood pressure did not return completely to normal, the hypertension was of more than 2½ years' duration in all but three, ranging from 1 month to 12 years. The difference in age and duration of hypertension between these two groups is striking and suggests a possible explanation for the difference in blood pressure response. In addition to a fall in blood pressure, these patients experienced marked improvement in clinical symptoms, physical findings, and laboratory abnormalities. Headaches, dizziness, and epistaxis dis-

appeared or subsided. Angina pectoris, if present prior to operation, lessened in severity. Electrocardiographic evidence of left ventricular hypertrophy subsided. Papilledema or hemorrhages and soft exudates receded in seven patients.

Preoperative differential renal excretion studies (Howard test) showed a significant difference in sodium and water excretion between the two kidneys in 12 patients whose blood pressure fell after surgery, whereas in six patients whose blood pressure fell, no significant difference was observed. The study was not performed or was unsuccessful in the remainder. In five of the patients who were studied again following surgery, the phenolsulfonphthalein excretion on the operated side was improved, and in four the sodium and water excretion was equal to or greater than that on the unoperated side, which had originally been the side with better excretion.

The blood pressure did not fall postoperatively in six patients. In two of these the stenotic lesion could not be completely repaired and areas of ischemic kidney probably persist. One patient (L.K.) whose blood pressure fell after bilateral segmental renal artery resection for fibromuscular hyperplasia, was found to have recurrent stenosis on the left side when her blood pressure rose abruptly 2 months later. Following left nephrectomy she was normotensive for 6 months and then her blood pressure returned to preoperative levels. Arteriography at this time revealed narrowing of the entire right renal artery considered to be inoperable. Moderately severe atherosclerosis was diagnosed on renal biopsy in a fourth patient and may explain the persistence of his hypertension. No definite explanation for the persistence of the hypertension is evident in the remaining two patients.

One patient died at surgery owing to cardiac arrest, and another patient died 2 days later from uncontrollable bleeding. Five other patients have died following surgery. One of these had rheumatic heart disease with uncontrollable atrial fibrillation, congestive heart failure, and multiple emboli to the brain, kidneys, and extremities. Another patient, who was in renal failure, had an extensive aortic aneurysm involving both renal arteries, and an attempt to improve his impaired renal circulation failed. A chronic duodenal ulcer perforated postoperatively in another patient with resulting peritonitis and shock. Sudden death, due in one case to a cerebral and in the other to a coronary occlusion, occurred in the remaining two. Four of these patients were 60 years or older, all had atherosclerotic lesions, and all but one of these cases required extensive operative procedures.

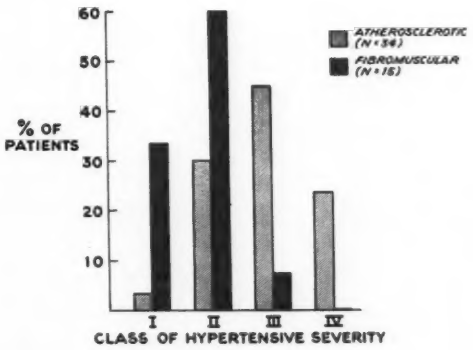

Figure 5

Comparison of hypertensive severity of patients with occlusive renal artery lesions due to atherosclerosis and fibromuscular hyperplasia of the media. Severity classification based on the level of the resting blood pressure and the degree of cardiac, fundal, and renal impairment resulting from the hypertension.

On pathologic examination of the stenotic arteries of patients whose blood pressure fell, 15 were proved to have atherosclerotic plaques as suggested by the radiographic pattern, while in nine patients the microscopic and radiologic picture was that of fibromuscular hyperplasia of the media. Figure 6 illustrates the microscopic appearance of an artery with fibromuscular hypertrophy in cross section, showing the intact intima and the widened media and adventitia composed of an excess of fibrous and muscular elements with resultant encroachment on the arterial lumen.

Examination of the 12 kidneys that were removed revealed hypoplasia (two cases), focal infarction (two cases), fibrosis and atrophy (four cases), and arteriolar sclerosis and chronic inflammatory infiltrate in four.

Table 6

Clinical Course of 38 Patients who Underwent Corrective Surgery

Patient	Age & sex	Duration of hypertension	Major arterial abnormality	Operative procedures	Duration of follow-up	Pathologic findings			Significant* difference in renal sodium & water excretion
						R kidney	L kidney	Renal artery	
Patients whose blood pressure returned to normal (14):									
P.A.	29 F	Less than 1 yr.	Bilateral RA stenosis L>>R	Bilateral RA exploration	30 mo. (no BP fall)	Bilateral capillary glomerulopathy (biopsy)		—	Yes R>L
	31	2½ yr.	LRA occlusion	L nephrectomy	1 mo.	—	30 Gm., multiple old infarcts	—	Yes R>L
A.C.	58 F	Less than 1 yr.	Hypoplastic R kidney and artery	R nephrectomy	6 mo.	80 Gm. atrophy	—	Athero.	Probably yes L>R (technical difficulties)
L.C.	18 F	Less than 2 yr.	LRA segmental stenosis	Spleno-LRA shunt	11 mo.	Normal renal tissue (biopsy)	Focal atrophy & fibrosis (biopsy)	FMH	Not measuerd
V.E.	37 F	Less than 1 yr.	RRA segmental stenosis with aneurysms	R nephrectomy	21 mo.	125 Gm. focal infarct	—	FMH	Yes—L>R
G.L.	47 M	Less than 2 yr.	RRA take-off stenosis	RRA endarterectomy	11 mo.	Focal interstitial fibrosis	—	Athero.	Yes—L>R
R.P.	44 F	9 yr.	LRA take-off stenosis	Spleno-LRA shunt	18 mo.	—	—	Athero.	Yes—R>L
D.R.	35 F	2 yr.	Bilateral RA segmental stenosis R>>L	RRA segmental resection	25 mo.	Arteriolar sclerosis (biopsy)	Normal renal tissue (biopsy)	FMH	Yes—L>R
A.R.	38 F	Less than 1 yr.	RRA segmental stenosis	RRA segmental resection	11 mo.	Chronic pyelonephritis (biopsy)	Mild, non-specific tubular degeneration (biopsy)	FMH	No
W.S.	36 M	1 yr.	Ao-iliac & LRA take-off stenosis	Ao-common iliac bypass graft; L nephrectomy	8 mo.	Arteriolar sclerosis (biopsy)	125 Gm. Arteriolar sclerosis & chronic pyelonephritis	Athero.	Yes—R>L
E.S.	46 F	Unknown—	Comp. segmen-	Ao-iliac, LRA	84 mo.	—	Arteriolar	Athero.	Not measuerd

			stenosis	graft; L nephrectomy		(biopsy)	chronic pyelonephritis		
E.S.	46 F	Unknown—? recent onset	Comp. segmental occlusion, abdominal ao. & LRA take-off stenosis	Ao-iliac, LRA endarterectomy	84 mo.	—	Arteriolar sclerosis (biopsy)	Athero.	Not measuerd
	53	Not hypertensive	LRA stenosis	L nephrectomy	1 mo.	—	173 Gm. mild arteriolar sclerosis	Athero.	Not measured
S.S.	17 F	8 yr.	LRA segmental stenosis & L kidney hypoplasia	L nephrectomy	4 mo.	—	58 Gm. hypoplasia	FMH	No
S.W.	33 M	1 yr.	LRA occlusion	L nephrectomy†	84 mo.	—	—	Athero.	Not measured
	40		RRA take-off stenosis ao.-iliac stenosis	RRA—endarterectomy	12 mo.	—	—	Athero.	Not measured
K.Y.	11 F	1 yr.	Hypoplastic R Kidney & RRA	R nephrectomy	11 mo.	37 Gm. Hypoplasia	—	Hypoplasia	No
N.Z.	22 F	7 yr.	RRA segmental stenosis	RRA segmental resection	10 mo.	Normal kidney bilaterally (biopsy)		FMH	No
Patients whose blood pressure decreased but not to normal (11):									
C.C.	36 M	16 yr.	Bilateral RA take-off stenosis	Bilateral RA endarterectomy	8 mo.	—	—	Athero.	Yes—R>L
R.F.	53 M	1 mo.	Ao. occlusion with LRA & RRA take-off stenosis	Ao-iliac graft L nephrectomy RRA endarterectomy	8 mo.	—	Chronic pyelonephritis with fibrosis & arteriolar sclerosis (not weighed)	Athero.	Not measured (technical difficulties)
A.H.	62 M	1 mo.	LRA stenosis	L nephrectomy	71 mo.	—	115 Gm.—Chronic pyelonephritis arteriolar sclerosis	Athero.	Not measured
R.L.D.	53 F	12 yr.	RRA take-off ao. & L iliac stenosis	RRA & iliac endarterectomy	21 mo.	Bilateral mod. arteriolar sclerosis (biopsy)		Athero.	Not measured
Z.M.	44 F	3 yr.	Bilateral RA segmental stenosis R>L	RRA segmental resection	7 mo.	Normal renal tissue bilaterally (biopsy)		FMH	Yes—L>R
M.N.	42 F	11½ yr.	RRA segmental stenosis	RRA segmental resection	12 mo.	—	—	FMH	No
F.P.	48 F	7 yr.	RRA occlusion	R nephrectomy†	6 mo. (no fall)	(not weighed) infarction	—	Athero.	Not measured
	48	7 yr.	LRA take-off stenosis	LRA endarterectomy	21 mo.	—	—	Athero.	Not measured

Table 6—(Continued

Table 6—(Continued

Patient	Age & sex	Duration of hypertension	Major arterial abnormality	Operative procedures	Duration of follow-up	Pathologic findings: R kidney	Pathologic findings: L kidney	Renal artery	Significant* difference in renal sodium & water excretion
Patients whose blood pressure decreased but not to normal (Continued)									
H.P.	49 F	6 yr.	RRA take-off & ao. stenosis	RRA & ao. endarterectomy	9 mo.	Bilateral arteriolar sclerosis (biopsy)		Athero.	No
E.V.	54 M	1 yr.	RRA take-off stenosis	RRA endarterectomy	19 mo.	—	—	Athero.	Yes—L>R but tech. difficult.
F.W.	61 M	3 yr.	RRA occlusion	R nephrectomy	9 mo.	65 Gm., arteriolar sclerosis, chronic pyelonephritis, fibrosis, atrophy	—	Athero.	Yes—L>R
J.W.	53 M	4 yr.	Bilateral RA stenosis—ao. aneurysm	Spleno-LRA shunt resection & replacement graft of ao. aneurysm	5 mo. (no fall)	Arteriolar sclerosis (biopsy)	—	Athero.	No
	53	4½ yr.	Residual inoperable RRA stenosis	R nephrectomy	2 mo.	100 Gm., focal atrophy mod. arteriolar sclerosis	—	Athero.	Yes—L>R
Patients whose blood pressure did not decrease (6):									
W.Ba.	53 M	6 mo.	Bilateral RA take-off stenosis	Bilateral RA endarterectomy	42 mo.	Bilateral moderately severe arteriolar sclerosis (biopsy)		Athero.	No
W.Br.	43 M	Less than 1 yr.	Bilateral RA take-off stenosis	Incomplete LRA endarterectomy	9 mo.	—	—	Athero.	No
E.D.	65 F	Unknown	RRA take-off stenosis	RRA endarterectomy	6 mo.	—	—	Athero.	No
C.H.	48 M	Less than 1 yr.	Complete occlusion of ao., bilateral RA take-off stenosis	Spleno-LRA shunt	4 mo.	Arteriolar sclerosis	—	Athero.	Yes—L>R
L.K.	35 F	18 yr.	Bilateral RA segmental stenosis	Bilateral RA segmental resection	2 mo.	—	—	FMH	No
			LRA stenosis	L nephrectomy	10 mo.	—	(not weighed) focal infarct chron. pyelonephritis	—	No
			bilateral RA take-off stenosis	endarterectomy spleno-LRA					

			bilateral RA take-off stenosis	endarterectomy spleno-LRA shunt				chron. pyelo-nephritis	
Patients who died during or after surgery (7):									
M.B.	59 M	1 yr.	Ao. aneurysm involving both RAs	Excision of aneurysm, replacement graft, bilateral RA endarterectomy	12 da.; (death from uremia)	Arteriolar sclerosis	Complete infarction (autopsy)	Athero.	Not measured
G.D.	44 F	6 yr.	Ao. occlusion, LRA take-off stenosis	Ao-femoral bypass graft bilateral RA endarterectomy	Death at surgery; irreversible cardiac arrest	Multiple healed infarcts both kidneys, mild arteriolar sclerosis (autopsy)		Athero.	Not measured
G.J.	72 M	11 yr.	Celiac axis superior mesenteric stenosis, RA not visualized	Ao., superior mesenteric, celiac axis & LRA endarterectomy	2 da.; (death from hemorrhage)	Bilateral mild arteriolar sclerosis (autopsy)		Athero.	Not measured
W.M.	67 M	11 yr.	LRA take-off stenosis	LRA endarterectomy	4 da.; (death from perforated peptic ulcer)	Bilateral arteriolar sclerosis (autopsy)		Athero.	No
W.P.	64 M	11 yr.	Bilateral RA stenosis	Bilateral RA endarterectomy	10 da.; (died from cerebral artery thrombosis)	Bilateral arteriolar sclerosis (autopsy)		Athero.	Yes—R>L
R.S.	60 M	5 yr.	Bilateral RA stenosis	Bilateral RA endarterectomy	1 mo.; (died from myocardial infarction)	No autopsy		Athero.	Not measured
A.W.	49 F	Less than 1 yr.	Ao. & LRA occlusion; RRA take-off stenosis	L nephrectomy RRA & ao. endarterectomy	6 da.; (died from multiple renal & cerebral emboli)	Recent infarction (autopsy)	Old infarction	Athero. & emboli from L atrial thrombus	Not measured

*Significant difference is defined as a 50 per cent difference in water and 20 per cent difference in sodium excretion.

†Operation performed at another hospital.

Abbreviations: RA, renal artery; LRA, left renal artery; RRA, right renal artery; Athero., atherosclerosis; FMH, fibromuscular hyperplasia of the media; Ao, aorta.

In the renal biopsies that were available, no consistent abnormality was detected. In some patients the kidney biopsy on the side of the arterial stenosis was normal and the opposite kidney showed arteriolosclerosis or nonspecific changes, while in others the reverse situation occurred or both kidneys showed the same changes.

Discussion

The demonstration of major abnormalities of the renal artery in 50 per cent of the selected hypertensive patients examined by arteriography suggests that hypertension secondary to renal ischemia is not a rare finding. This figure approaches the results of Blackman, who reported finding obstructing atherosclerotic plaques projecting into the lumen of one or both renal arteries in 86 per cent of 50 hypertensive patients examined at autopsy and in only 10 per cent of 50 nonhypertensive patients examined concurrently.[38] The incidence of severe complications from arteriography in this study was relatively low, and was further decreased by avoiding general anesthesia and using the retrograde transfemoral approach. Aside from the occasional problem of retroperitoneal bleeding, the primary disadvantage of the translumbar technic has been the periaortic inflammatory reaction, which may make subsequent surgical dissection difficult. Preliminary experience with retrograde catheterization following puncture of the femoral artery has demonstrated that this technic gives equally satisfactory renal artery visualization and avoids the local complications of aortic puncture. At the present time this method is preferred unless there are extensive occlusive lesions in the aorta or iliac or femoral vessels. The potential complications of arteriography will probably never be completely avoided, but the chances of finding a curable lesion warrant the risk of the procedure, since both the diagnosis and the preoperative anatomic localization of the abnormality can be obtained only by arteriography.

Routine visualization of the renal artery in all hypertensive patients is not practical, therefore the question arises of how to select those patients most likely to have demonstrable abnormalities by arteriography. As a group, the patients with arterial lesions in this series did not differ in their clinical appearance from the general population of hypertensive patients. In many patients the hypertension was well-controlled with drugs; both mild and severe cases were represented, as were patients in all age groups, with and without a family history of hypertension. The results of renal function tests were normal in most of the patients, and in 17 per cent the excretory urograms were also normal. In most of the patients with major renal artery abnormalities, multiple indications for arteriography were present, and 68 per cent had either recent onset or increase in hypertension, and 80 per cent had a bruit; in a few, only one indication, such as severe hypertension or atherosclerosis of the abdominal aorta, was present. Although a positive Howard study usually pointed to a unilateral arterial lesion, a negative study was often associated with bilateral abnormalities and thus did not help to differentiate these patients from those with normal renal arteries. None of the indications for arteriography was always associated with positive arteriographic findings, nor was the absence of any one always associated with a normal arteriogram. Perera and Haelig's suggestion that the hypertension secondary to renal artery stenosis is usually severe and difficult to control is not borne out by our findings.[19] Our experience to date indicates that by doing arteriograms in individuals with unexplainable recent onset or exacerbation of hypertension, papilledema, an epigastric bruit, atherosclerosis of the abdominal aorta, or disparity in renal size or function, one is likely to discover the majority of patients with arterial abnormalities. However, the variety of clinical patterns associated with renal artery abnormalities suggests that at present there are no completely reliable clinical methods to exclude the possibility of an arterial lesion. The true frequency of this abnormality will not be known until a series of consecutive hypertensive patients is studied with arteriography.

The classification of the radiologic findings as atherosclerotic, fibromuscular hyperplasia, or hypoplasia of the renal artery appears jus-

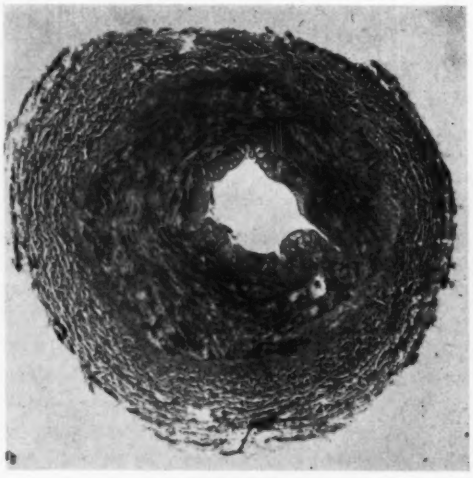

Figure 6A

Cross section of the renal artery through an area of fibromuscular hyperplasia. The marked decrease in the arterial lumen is contrasted to lumen in figure 6B. Hematoxylin and eosin stain.

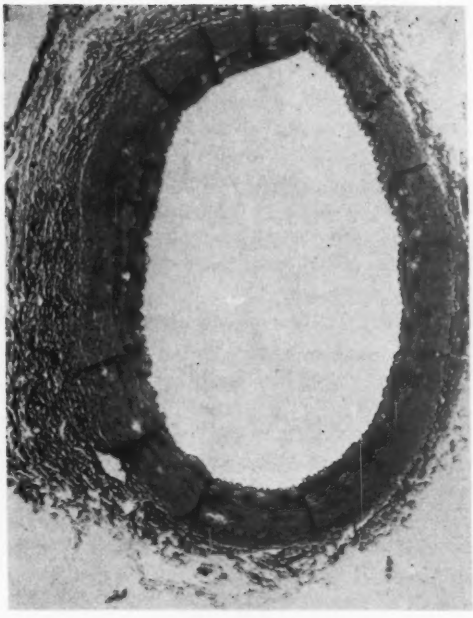

Figure 6B

Cross section through a segment of normal renal artery. Hematoxylin and eosin stain.

tified on the basis of the observations at operation and pathologic examination of the resected specimens. Little is known about the pathogenesis of fibromuscular hyperplasia, nor do we know whether the pathologic process will recur after resection or extend to other vessels. Repeat arteriograms on operated and unoperated patients with minimal lesions of fibromuscular hyperplasia will help to increase our understanding of this process. The observation that most of the patients with fibromuscular hyperplasia were relatively young women* with mild hypertension again stresses the importance of suspecting renal artery stenosis even in patients with mild hypertension and among the group considered as representing classical essential hypertension. The atherosclerotic lesions appeared both in patients with longstanding hypertension in whom atherosclerosis was perhaps accelerated by the hypertension and in patients with generalized atherosclerosis without previous hypertension. The mortality following surgical correction in this group of patients, many of whom also had cerebral and coronary atherosclerosis, was relatively high.

The classification "minor lesions" raises the question: how stenotic must an artery be, by radiologic examination, to justify surgical repair? In the absence of quantitative pressure and flow measurements, this decision depends on a qualitative appraisal by the experienced surgeon and radiologist. However, continued observation and serial examinations will be necessary to clarify the prognostic importance of minor arterial abnormalities. Likewise, the presence of an isolated aneurysm of the renal artery without stenosis, although reported in nonhypertensive patients, [39, 40] could be associated with hypertension, and such cases have been reported cured of their hypertension following suitable vascular repair. At this point one might speculate whether the patient (P.A.) whose radiologic abnormalities were not confirmed at the initial arteriotomy, developed progression of the original minimal process with eventual complete occlusion and secondary thrombosis

*We have since observed a similar lesion in an 11-month-old boy, and male cases have been reported in the literature.[27]

of the renal artery. This would explain the marked decrease in renal size and unquestionable evidence of renal infarction 2½ years later. If the process represented by minimal radiologic abnormality is a progressive one, at what stage is vascular repair indicated, and when does nephrectomy become inevitable because of irreversible renal changes?

The type of surgical procedure used in each patient depended on the site and extent of the arterial lesion. These problems are largely technical and depend on the availability of a skilled vascular surgeon. Reconstruction is particularly difficult in the presence of associated atherosclerotic disease of the aorta and its major branches. Whenever possible, a stenotic segment was resected, a plaque removed, or a shunt performed around the lesion in order to save the kidney. The postoperative improvement in phenolsulfonphthalein, water, and sodium excretion in many cases, suggesting that renal function had improved following restoration of renal blood flow, justifies these vascular reconstructive procedures, even though they are associated with a greater operative risk than simple nephrectomy. However, the demonstration of arteriolar sclerosis in some of the renal biopsies from kidneys distal to an arterial stenosis, leads to speculation regarding the "protected" kidney theory reported by other authors.[20-22] Likewise, the postoperative blood pressure fall in all of the patients who underwent simple nephrectomy suggests that the "unprotected" kidney may not be irreparably altered by the hypertension, especially when it is of short duration, and may be capable of maintaining both normal renal function and restoring normotension.

It is still premature to formulate definite conclusions from the postoperative fall in blood pressure observed so far. But the results thus far have been encouraging, especially in the younger age group and in the patients with fibromuscular hyperplasia. The postoperative fall in blood pressure in 25 of the 31 surviving patients, with a sustained fall to normal in 14 of the 25, is very gratifying. These patients would otherwise have been committed to a lifetime of expensive drug therapy, often of limited efficacy. In addition to a fall in blood pressure, these patients have lost many of their symptoms. In several, the abnormal electrocardiogram has returned to normal, and the fundal changes of advanced disease have disappeared.

Although most of the patients whose blood pressure returned to normal had a relatively short history of hypertension, a long history of hypertension was not incompatible with a complete return to normal following operation. In patients with a correctible lesion we were not able to find any consistent preoperative indications on which to predict whether the blood pressure would fall after surgery. All patients with a significant difference in renal sodium and water excretion experienced a postoperative fall in pressure, but patients with unilateral lesions and equal renal excretion as well as patients with bilateral lesions also had a fall in blood pressure. The Howard test is, therefore, useful both in diagnosis and prognosis only when the results are positive.

In the patients in whom the blood pressure was not lowered after surgery, the presence of an inoperable lesion or moderately advanced arteriolar sclerosis on renal biopsy are probable explanations for the surgical failure. The routine performance of bilateral renal biopsies is justified as a prognostic aid, although the isolated presence of arteriolosclerosis should not be considered a contraindication to vascular reconstruction.

The postoperative mortality in our group of patients is high compared to the figures from other medical centers,[26, 28] in part because we attempted to explore the scope and applicability of reconstructive arterial procedures even in poor-risk patients. It is now apparent that the greatest mortality occurred in the elderly arteriosclerotic patient and during the period of development of operative technics. Should increasing experience not be reflected in a reduction of operative mortality in this elderly group, simple nephrectomy may be the preferable procedure in those with unilateral lesions.

Summary

Historically, the awareness of renal artery narrowing as a curable cause of hypertension

has evolved gradually, highlighted especially by Goldblatt and Poutasse. The increasing use of renal arteriography over the past 8 years in this hospital has yielded a total of 70 patients with renal artery abnormalities out of 110 hypertensive patients examined.

In order to select the hypertensive patients most likely to have demonstrable arterial lesions, certain indications for arteriography were used. Most useful among these were the presence of an epigastric bruit, malignant hypertension, atherosclerosis of the abdominal aorta, and recent onset of hypertension. However, no one indication was always present in patients with lesions or always absent in those without abnormalities.

Of the 70 patients with renal artery abnormalities, 54 were considered to represent sufficient renal artery stenosis to be potential candidates for surgical correction, while 16 had minor renal artery abnormalities. Atherosclerotic lesions occurred in 63 per cent of the patients with significant lesions, fibromuscular hyperplasia in 28 per cent, unilateral renal artery hypoplasia or atrophy in 7 per cent, and one case had embolic renal artery occlusion. Fifty-four per cent of all patients with significant lesions had bilateral disease. The patients with atherosclerotic lesions and those with fibromuscular hyperplasia differed markedly in sex distribution, age, and severity of hypertension. It is suggested that the retrograde transfemoral catheterization technic may be associated with fewer complications in patients without extensive occlusive atherosclerotic disease of the aorta, and iliac and femoral arteries.

At operation the radiologic findings were confirmed in all but one patient. Corrective surgical procedures were performed in 38 patients, including nephrectomy, endarterectomy, segmental resection with reanastomosis, and splenorenal arterial shunt. Of the 31 patients who survived, 25 (81 per cent) had a postoperative fall in blood pressure, 14 to normal, in addition to improvement in clinical status. The follow-up period, however, is not yet sufficiently long to permit definite conclusions. Seven patients died; most of these had bilateral renal artery disease and extensive atherosclerosis of the cerebral and coronary arteries.

Divided renal function studies were of limited diagnostic value because of the high incidence of bilateral lesions. In all patients with significant differences in renal sodium and water excretion, a postoperative fall in blood pressure occurred, but the same number of patients with equal bilateral excretion also had a fall in blood pressure.

The importance of suspecting renal artery lesions in hypertensive patients regardless of age, severity of hypertension, or renal function is stressed. The question is discussed whether all patients with sustained hypertension should undergo arteriography. Although further studies to determine the true prevalence of occlusive renal artery lesions in the hypertensive population are in order, the fact that 50 per cent of our 110 patients had occlusive lesions and 60 per cent of the operated cases had a fall in blood pressure attests not only to the prevalence of the lesion but also to its potential curability.

Acknowledgment

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Surgery in Complete Occlusion of the Internal Carotid Artery

By A. J. GUNNING, F.R.C.S., AND R. W. ROSS RUSSELL, M.D., M.R.C.P.

IT IS WELL KNOWN that vascular disease of the brain and the retina is often associated with occlusive disease of the carotid arteries. It is now possible in many cases to remove the occlusion, and such operations are being performed with increasing frequency. The technical results of operations on the common carotid, innominate, and subclavian arteries are highly satisfactory both for stenosing and complete occlusions, and at the origin of the internal carotid artery stenosing lesions are again readily operable.[1, 2] It is not yet possible to assess the functional results of these operations, as many of the patients coming to surgery have little or no neurologic disability, and the operation is performed in the hope of preventing future vascular accidents.

In patients with total occlusion in the region of the carotid bifurcation the results of surgery, both technically and functionally, are even more uncertain and for this reason we report our experience from the period of 1958 to 1960 in 15 such cases in whom surgical treatment was undertaken.

Clinical Features

There were 10 men and five women whose ages ranged from 33 to 75 years. Twelve patients presented with a hemiparesis, two with monocular visual symptoms, and one with focal seizures. The onset was associated with loss of consciousness in only two patients, and previous transient symptoms were remarked upon by seven patients.

There were no unusual features on clinical examination; the diastolic blood pressure was over 120 mm. Hg in only one patient, and one patient had mitral stenosis and atrial fibrillation. A palpable diminution or absence of the appropriate carotid pulse was noticed in eight patients. Two patients had a bruit over the occluded carotid and several others had systolic bruits over the carotid bifurcations on the other side. Ptosis and meiosis of the pupil on the side of the carotid lesion were noticed in four patients, but facial sweating was unaltered. One patient showed unilateral optic atrophy, and three patients seen during an attack of blindness showed retinal edema and arterial occlusion. In one patient friable microemboli were seen passing through the retinal vessels during an attack of monocular blindness.[3]

A hemiparesis, of variable severity, was present in 12 patients; in all, the arm and face were more severely affected than the leg. Six had a homonymous hemianopsia.

One patient had the unusual combination of internal carotid occlusion on one side with ophthalmic artery occlusion on the other, due to multiple embolism from an atrial myxoma.

Pressure Measurements of Ophthalmic Artery

In 13 patients ophthalmic artery pressures were measured with the Bailliart ophthalmodynamometer, and results are shown in figure 1. Most cases showed some diminution of pressure on the affected side, the most marked difference appearing in systolic rather than diastolic readings and in early rather than late cases.

After operation, in which pulsatile back flow was established, ophthalmic pressures returned to normal (four cases).

Angiographic Findings

Percutaneous puncture of the common carotid artery was done in thirteen patients. In the remaining two patients the diagnosis was made on the absence of the common carotid pulsation. Exposures were taken on completion of injection and 2 and 6 seconds thereafter.

The criterion of carotid occlusion was ab-

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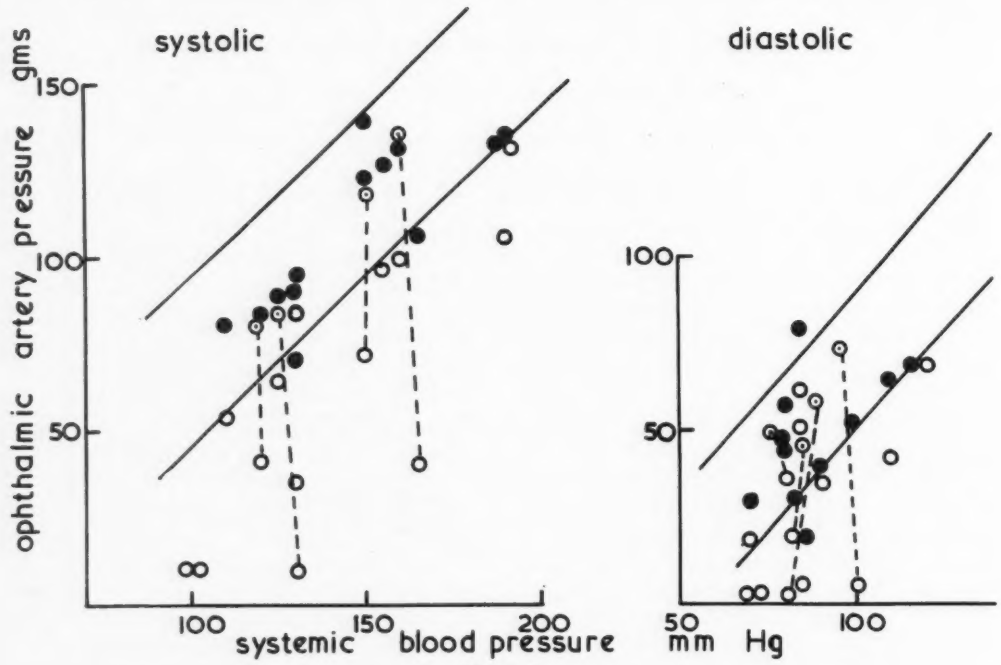

Figure 1

Ophthalmic artery pressure measurements on 13 patients. The lines indicate the range of normality (95 per cent confidence limits) for patients over 50 years. Closed circles, normal side; open circles, occluded side. Postoperative change indicated by dotted lines.

sence of filling of the intracranial artery, and there were two kinds of angiographic appearance.

Group I. Complete hold-up of the dye occurred in the internal carotid artery within 1 to 3 cm. of the origin (eight cases). Collateral vessels were usually well developed.

Group II. Apparent complete hold-up of the dye occurred in the first part of the internal carotid artery. In later films the dye was seen filling or partially filling the upper part of the artery as far as the base of the skull (five cases). Collateral vessels were not seen in this group.

This appearance indicates an occlusion of the upper part of the internal carotid that is not quite complete. When the artery is blocked at this site, retrograde thrombosis tends to occur throughout the length of the vessel to within a short distance of the origin. The final appearance is of complete occlusion at the origin of the artery, irrespective of the initial site of the thrombosis.

In two cases belonging to angiographic group II, with an intracranial occlusion and slow flow up the artery, it was possible to verify the site of the block by angiography on the operating table, dye being injected directly into the cervical part of the internal carotid artery.

Postoperative angiograms were done on only two patients as the restoration of normal carotid pressure was checked more easily by ophthalmodynamometry. There were no ill effects after arteriography.

Pressure Measurements of Carotid Artery

Pressure measurements were attempted on five occasions by a Statham strain-gage manometer, the artery being punctured with a no.-1 needle. It was not found possible to record the pressure on both sides of a complete occlusion at the origin of the internal carotid

Table 1

Results of Operation (Fifteen Carotid Arteries Explored)

A. Pulsatile backflow established	5	
Patent postoperatively (ophthalmodynamometer)	4	(Case 4 not examined)
Subsequent rethrombosis (detected by palpation)	3	Case 4. Rethrombosis at 5 days Second operation; thrombosed again; no change Case 11. Rethrombosis at 2 days; died Case 10. Rethrombosis at 4 weeks; died
No subsequent rethrombosis	2	Case 2. Slight improvement postoperatively; died 3 months later from cancer; carotid patent at autopsy Case 6. Complete recovery (9 months)
B. Backflow not established	10	
Improved on follow-up	5	Case 1. Complete recovery 3 years Case 3. Complete recovery 2 years Case 7. Improved, working 9 months Case 9. Improved, at home 6 months Case 13. Improved, no more attacks 3 months
Unchanged or worse	3	Case 5. Working 18 months Case 8. Working 1 year Case 14. In hospital 6 months
Died	2	Case 12. One week postop.; autopsy, carotid blocked at syphon Case 15. Died postoperatively; autopsy, multiple emboli

owing to thrombosis in the distal portion of the artery. In cases belonging to angiographic group II, where the occlusion occurred at the base of the skull, measurements gave confirmatory evidence of a distal occlusion, the pressure being equal in internal and common carotid arteries apart from slight damping in the distal record.

Operation

Through an incision parallel to the sternomastoid muscle, from the tip of the mastoid process to the level of the cricoid cartilage, the common carotid artery and its two branches were exposed. Approximately 7 cm. of the internal carotid artery were isolated. The lower end of the obstruction was usually at the point of bifurcation. No effort was made to do a temporary bypass of the obstruction.

Before opening the artery heparin (5,000 to 10,000 units) was given intravenously and allowed to circulate for 1½ to 2 minutes before clamping the common and external carotid arteries with Glover's multitoothed clamps. An incision was then made into the termination of the common carotid artery, along the bulb and into the internal carotid artery. If there was any back bleeding from the internal carotid artery, the artery was clamped. A formal endarterectomy was then done, and the thrombus together with the thickened atheromatous intima was easily separated and removed. Downwards into the common carotid the intima was thin and was divided. Distally, however, the thickened intima extended well up the internal carotid artery. The cut edges of the intima were sutured back to the media to prevent dissection of the coats when the flow of blood was reestablished. Before suturing the incision with 6.0 black silk a sucker and corkscrew reamer were passed up the internal carotid artery in an attempt to remove thrombus in the upper reaches of the artery. In early cases the artery was found to contain a soft, black thrombus. It has been our experience that suction alone was seldom successful in removing the clot, and we relied on a corkscrew reamer. The instrument was gently rotated into the open internal carotid artery for a short distance and then removed. A portion of thrombus was usually brought out with it, and the process was repeated rotating the reamer farther up the artery until the base of the skull was reached. By this means the last piece of a propagated thrombus was sometimes successfully removed and pulsatile back flow was es-

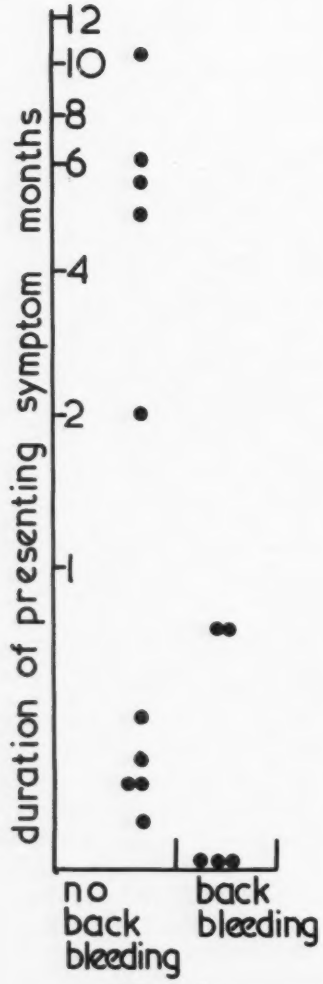

Figure 2

Duration of symptoms in technically successful cases and in those found to be inoperable.

tablished. The wound in the neck was closed in layers.

Results of Operation

A summary of the follow-up information is given in table 1 and shows that technically successful operations were achieved in five of 15 patients. Three of the carotid arteries subsequently thrombosed, although all five patients had been maintained on anticoagulants during the period in hospital. Half the patients in whom operation was unsuccessful showed some improvement postoperatively and two were completely normal 3 years later. Of the four patients who died three were comatose and gravely ill before operation, one (case 10) had only a moderate hemiparesis and was unquestionably made worse by operation. This may have been due to an embolic blockage of an intracranial vessel or to a short period of hypotension during operation.

Pathology

The pathology of the arterial occlusion was deduced from inspection of the artery at operation, from histologic examination of the endarterectomy specimen or from autopsy. In eight cases there was evidence of extensive atheroma at the origin of the internal carotid, and atheromatous plaques were removed by blunt dissection. All these cases showed recent thrombus on the surface of the plaque, and it appeared likely that the last stage of obliteration of the arterial lumen was one of thrombotic occlusion. Recent thrombus extended upward into the cervical portion of the internal carotid (five cases) and downward into the common carotid (two cases). It also extended into the external carotid artery on two occasions and probably into the ophthalmic artery on one occasion. In two cases the occlusion was embolic, one a case of mitral stenosis and the other of atrial myxoma. In both, the embolus impacted in the intracranial portion of the internal carotid and the angiogram showed apparent occlusion near the origin in early view, with delayed flow up the cervical carotid that was visible in the later films.

In one case thrombotic occlusion occurred 12 hours after an injury to the face and neck. The patient was a young man with minimal atheroma. In one case multiple arterial thrombosis including both femoral and one internal carotid occurred over the course of 6 weeks. There was no evidence of arteritis or of blood disorder, and atheroma was only moderate. In two cases belonging to angiographic group II, the internal carotid artery was narrowed and nonpulsatile in its cervical course. There was no evidence of atheroma or thrombosis at the bifurcation on opening the artery, and only slight back-bleeding occurred. Both these patients had long histories, and in one the

onset of symptoms may have been related to a gunshot wound of the neck 20 years previously. It is also possible that the internal carotid artery was congenitally hypoplastic.

Discussion

The clinical observations in the present series are in accord with other reports on larger numbers of patients.[4] It is often impossible to diagnose a carotid thrombosis on clinical grounds alone. The combination of ocular and cerebral symptoms was present on six occasions and seven patients described transient ischemic attacks in the months or years preceding the major stroke. Carotid pulsation in the neck was palpably diminished in eight patients including two with common carotid occlusion. Carotid bruits were variable; the presence of a bruit did not exclude a total occlusion. Four patients had a partial Horner's syndrome but this was not correlated with duration of obstruction and occurred in both acute and chronic cases. It was presumably due to an interruption in the blood supply to the sympathetic trunk. Angiography showed an unexpectedly large proportion of cases in which the obstruction appeared to start at the base of the skull, and the appearances in these cases of a slow laminar flow of dye up the stagnant or nearly stagnant vessels are noteworthy. These findings are not diagnostic of carotid occlusion but may occasionally be seen affecting both carotid arteries in acute hydrocephalus from tumor or subarachnoid hemorrhage.[5]

When considering the results of treatment in extracranial carotid disease it is helpful to distinguish between carotid narrowing and carotid occlusion. Narrowing is extremely common and occurs in about one third of random autopsies, frequently affecting more than one of the main vessels.[6] Most cases are symptomless but when symptoms do occur they are often transient and repetitive, both in the eye and in the cerebral hemisphere.[7] The pressure in the upper part of the carotid artery measured directly at operation or indirectly by ophthalmodynamometry is usually normal, and histologic examination of the intima removed by endarterectomy usually shows fresh thrombus on a basis of atheroma. It is probable that many of the transient symptoms suffered by these patients are due to embolism from a diseased portion of artery, a process that is known to occur in other situations, e.g., the subclavian artery in association with a cervical rib.[8] If the diseased intima can be removed by endarterectomy, the transient attacks may cease. Assessment of such cases is difficult, however, since attacks may cease spontaneously, and also because patients are often maintained on anticoagulants.[9] If embolism is frequent and if the area of stenosis cannot be removed, it may be advisable to ligate the internal carotid, provided a good cross circulation can be demonstrated angiographically.

When a partial occlusion becomes complete, the symptomatology and approach to treatment are different. Here the brain is entirely dependent on collateral vessels and the pressure in the upper part of the affected carotid artery is reduced, particularly when the occlusion occurs rapidly as when the artery is ligated.[10, 11] Under these circumstances the collateral blood flow to the hemisphere on the affected side is liable to become insufficient when the systemic blood pressure falls.[12] Many patients undergo spontaneous carotid occlusion without symptoms and the lesions may be discovered incidentally at autopsy; in others, possibly those with more advanced arterial disease, the collateral vessels are inadequate and a hemiplegia ensues.

Pulsatile backflow, which is the prerequisite of a technically successful operation, was achieved in five of 15 patients, about the same proportion of successful results as reported by others in total internal carotid occlusions.[1, 7, 13] In the remainder, either the site of the occlusion was inaccessible or the thrombus had organized and extended throughout the length of the vessel. The successful operations were all carried out within a few days of the onset of hemiparesis (fig. 2) and it is possible that had the other patients been seen earlier, most of the operations would have been successful.

Functionally, results were even less impressive. In the present series two of the tech-

nically successful operations were followed by some postoperative improvement and one returned completely to normal, but many of these with inoperably occluded arteries also showed improvement. It is not surprising that thrombendarterectomy has little or no influence on recovery from existing symptoms, since the brain quickly suffers irreversible changes as a result of ischemia, and it follows that the only justifiable reason for operating on a completely occluded internal carotid is the belief that the prognosis with regard to further strokes will be improved if four instead of three patent vessels are supplying the brain. When one artery is severely narrowed by atheroma there is a probability that the other arteries (and other parts of the same artery) will also be affected, and this may possibly be a limiting factor in the development of collateral vessels. However, the incidence of cerebral infarction following carotid ligation is no higher in arteriosclerotic patients than in young patients.[14]

On the other hand, the not infrequent recurrence of thrombosis following endarterectomy, the fact that total occlusion takes place by thrombosis, and the possibility of embolism of loose thrombus during operation or at the time when total occlusion is taking place all suggest that the medical control of thrombosis might be of more benefit than surgery. Prothrombin inhibitors of the coumarol type seem to be doubtfully effective in controlling arterial thrombosis (three arteries in the present series rethrombosed while the patient was on adequate treatment with phenindione) and a more potent antithrombotic agent possibly with fibrinolytic or antiplatelet action is urgently needed.

Summary and Conclusions

The clinical features, findings on investigation, and results of operation are reported on 15 cases of complete thrombotic occlusion of the internal carotid artery. Backflow was established in five cases but no additional clinical improvement was noted when these cases were compared to others in whom operation was unsuccessful.

We cannot recommend surgery at the present time to patients with a moderate or severe hemiplegia associated with a complete angiographic block, with the prospect of relieving existing cerebral ischemia. It seems justifiable only as a possible insurance against further strokes, and its effectiveness in this regard is unknown.

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Supravalvular Aortic Stenosis

By J. C. P. Williams, M.B., B. G. Barratt-Boyes, M.B., and J. B. Lowe, M.B.

BEFORE Denie and Verheugt (1958)[1] drew attention to the possibility of diagnosing supravalvular aortic stenosis from the characteristics of the pressure tracings across the aortic valve region, there had been only autopsy reports of 17 cases with supravalvular obstruction. Fourteen of these earlier accounts concern bands or membranes stretching across the aortic lumen[2–10] and only three previous cases[11–13] are strictly comparable to Denie and Verheugt's patient, in whom the obstruction was due in part to hypertrophy of the media just above the sinuses of Valsalva and in part to constriction of the aortic wall at the same level. This patient presented the usual features of valvular or subvalvular aortic stenosis and the true condition was not recognized until operation. Denie and Verheugt commented that "as surgical correction of the aortic stenosis becomes more commonplace, . . . these anomalies may well be encountered more frequently." Subsequently, Morrow et al.[14] reported three similar cases, of which two were unsuspected until operation but one was diagnosed preoperatively by left heart catheterization. Angiocardiograms taken after retrograde left ventricular catheterization in two further cases were published by Hanson et al.[15] and by Dotter and Gensini,[16] and with the aid of cardiopulmonary bypass McGoon et al.[17] and Senning[18] have successfully relieved obstructions of this type.

Four new instances of this anomaly to which the term supravalvular aortic stenosis is becoming specifically applied are now reported. In three patients, who otherwise had the signs of valvular or subvalvular stenosis, the correct diagnosis was suggested before investigation by the close facial resemblance they bore to the fourth patient, who had been found to have supravalvular stenosis at operation. All four patients are mentally deficient and the association of supravalvular stenosis with the physical and mental characteristics here described may constitute a previously unrecognized syndrome.

From the Green Lane Hospital, Auckland, New Zealand.

Clinical Features

The patients, three female and one male, are aged 7 years (E.C.), 7 years (P.W.), 12 years (H.B.), and 11 years (J.S.). Their sexual characteristics are normal and in agreement with the leukocyte nuclear sex. Although mentally retarded they are receiving a limited education at special schools and they have sufficient understanding to have acquired normal social habits. Their intelligence quotients (Stanford-Binet) are 72, 67, 42, and 67, respectively.

Their facial resemblance, less strikingly shown in figures 1 and 2 than in real life, appears to derive largely from soft-tissue similarities, no common abnormality having been found in roentgenograms of their skulls. The faces are full, the foreheads broad, the eyes set well apart, the cheeks heavy and dependent, the mouths wide, and in some the lips are pouting. The chins, however, are pointed. Some have prominent ears and some have malocclusion of the teeth. Although there are clearly differences from face to face, the above features in varying degree combine to give the patients a similarity of appearance not easily defined but evident to their parents and the subject of comment by casual observers.

All the patients have siblings and, while they share with these siblings some family features, their own peculiarities of appearance are emphasized when they are seen in a family group (fig. 3). No other cases of congenital heart disease are known in the families. The parents were born in widely separated parts of the world, and there are no known family relationships.

The mothers were well during the pregnancies. At birth the three girls weighed only 5 lb. (E.C.), 4 lb. (P.W.), and 5 lb. (H.B.), and the boy (J.S.), although weighing 7 lb. 4 oz. at birth is said to have gained only 2 lb. in the first year. Except for H.B. they have remained below average weight for age.

Figure 1

Group photograph of four patients with supravalvular stenosis. Back row, H.B. and J.S. Front row, P.W. and E.C.

Figure 2

Profiles of P.W. (left) *and E.C.* (right).

No patient gave a history of limitation by cardiac symptoms, and in none was a heart defect suspected before the discovery of a murmur during a routine examination. In each the physical findings were similar to those found in valvular or subvalvular stenosis. There was a thrusting left ventricular apex beat and, in the aortic area, a loud systolic ejection murmur that was conducted to the carotids. Neither the peripheral pulse nor the respiratory variation of splitting of the second heart sound was abnormal. In no case was there an early systolic click or an early diastolic murmur.

The electrocardiograms (fig. 4) and the appearances in the chest roentgenograms were consistent with the presence of left ventricular hypertrophy. The ascending aorta was not prominent in any instance.

Pressure gradients across the aortic valve were not obtained in one patient (E.C.) until operation for suspected valvular stenosis; in the other patients gradients were recorded either by retrograde left ventricular catheterization via the right radial artery (J.S.), or by percutaneous left ventricular puncture (P.W., H.B.). In each case continuous pressure tracings during passage of the catheter between high aorta and low left ventricle showed a rise in systolic level a short distance above the aortic valve (fig. 5). The systolic gradients across the supravalvular stenosis were 100 (E.C.), 84 (J.S.), 68 (P.W.), and 38 mm. Hg (H.B.). In one case (E.C.) there was also a systolic gradient of 66 mm. Hg across the subaortic region of the left ventricle.

Angiocardiograms were taken in two patients (P.W., H.B.) at the time of left ventricular puncture (fig. 6). In each there was a localized narrowing of the lumen of the ascending aorta. Beyond this constriction the aorta returned to a normal caliber without developing a transitional "post-stenotic" dilatation. Large coronary arteries were displayed. The coronary ostia were at different levels, the right being the higher and lying close to the constriction.

At operation on E. C. (December 10, 1959) the stenosis was found to lie immediately distal to the sinuses of Valsalva, and the right coronary artery was dilated and arose immediately below the site of constriction. The stenosis could be seen externally as a localized narrowing of the aorta, while internally the lumen was further reduced by a bulky ridge of tissue projecting circumferentially from the aortic wall. Adjacent to the right sinus this ridge lost its attachment to the aortic wall and stretched across the lumen to create a secondary slit-like orifice. The aortic valve was tricuspid, the leaflets were normal except for slight thickening at their line of attachment to the aortic wall, and no subvalvular membrane was seen. Beyond the stenosis the ascending aorta gradually widened over a distance of 2.5 cm. to reach a normal diameter as it passed beyond the pericardial reflection. The lumen of the aorta was successfully enlarged by excising the subintimal ridge and inserting a pear-shaped Teflon patch into the aortic wall at the site of the constriction. The systolic pressure gradient between high and low ascending aorta was abolished. No attempt was made to correct the subvalvular obstruction, which it was thought might be due to muscular hypertrophy and might decline with the reduction in left ventricular pressure load.

In J.S., also, the supravalvular stenosis has been successfully relieved by the insertion of a Teflon patch into the aortic wall at the site of constriction, which, as in the previous case, lay just above the origin of the dilated and tortuous right coronary artery. Although the aortic wall was thickened in the region of the constriction, the aortic lumen was not further reduced by a projecting ridge.

Discussion

The clinical findings in our four cases were indistinguishable from valvular or subvalvular stenosis and, as others have commented,[1, 14] it may not be possible to differentiate these three conditions on clinical grounds alone. In our cases there was no dilatation of the ascending aorta in the chest roentgenogram but, since the ascending aorta is not always prominent in valvular or subvalvular stenosis, this appearance is not diagnostic. The absence of aortic dilatation may, however, serve to distinguish between supravalvular aortic stenosis and supravalvular membrane, for in the sole reported case[19] of this closely allied condition the ascending aorta was grossly dilated. In two cases of supravalvular stenosis associated aortic regurgitation was caused by tethering of the aortic cusps to the constriction ring.[1, 14] The presence of this complication might suggest the correct diagnosis, since significant incompetence is unusual in congenital aortic stenosis and is uncommon in subaortic stenosis when there is absence of dilatation of the ascending aorta.

Initially all our cases were believed to have aortic or subaortic stenosis and the first of the series (E.C.) was submitted to operation with this diagnosis. When the true condition was disclosed, patients with similar abnormalities of facial appearance believed to have aortic stenotic lesions were recalled for investigation and all three proved to have supravalvular aortic stenosis. The confirmation of the diagnosis in these circumstances suggests that supravalvular stenosis should be strongly suspected when mentally retarded patients with the facial features here described present the signs of a stenotic aortic lesion. In addition to the other common features all our patients had blue irises and their retinal vessels were unusually tortuous resembling those found in association with coarctation of the aortic isthmus (fig. 7).

Other physical abnormalities are present in three patients. H.B. is the most severely affected. She has prognathism, a marked thoracic kyphoscoliosis, and poor muscular coordination. When younger, she required

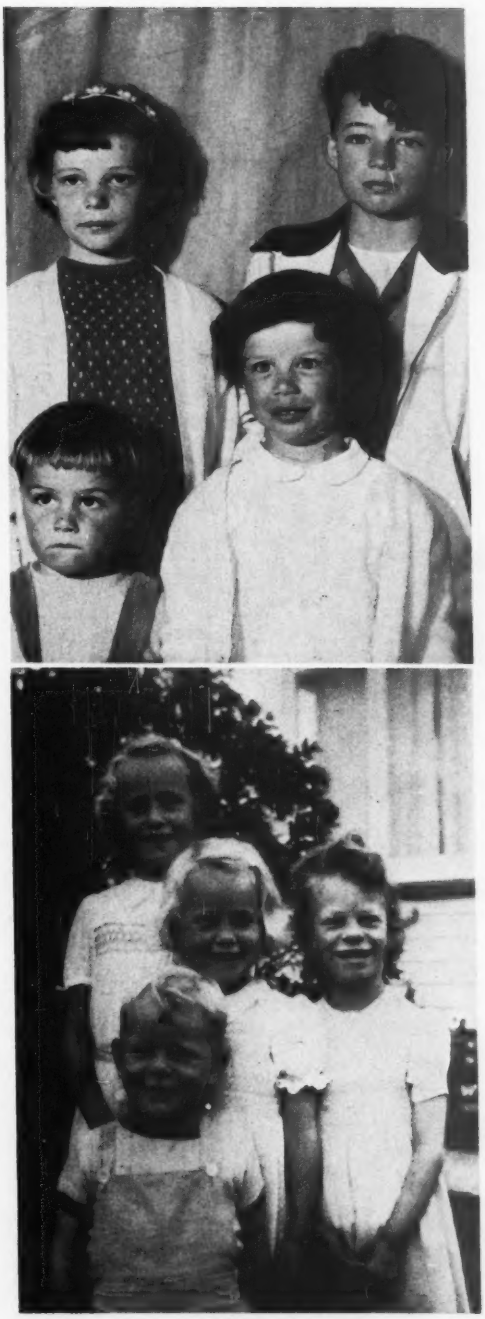

Figure 3

The unusual appearance of E.C. (top) *and H.B.* (bottom) *is emphasized when they are seen with their siblings.*

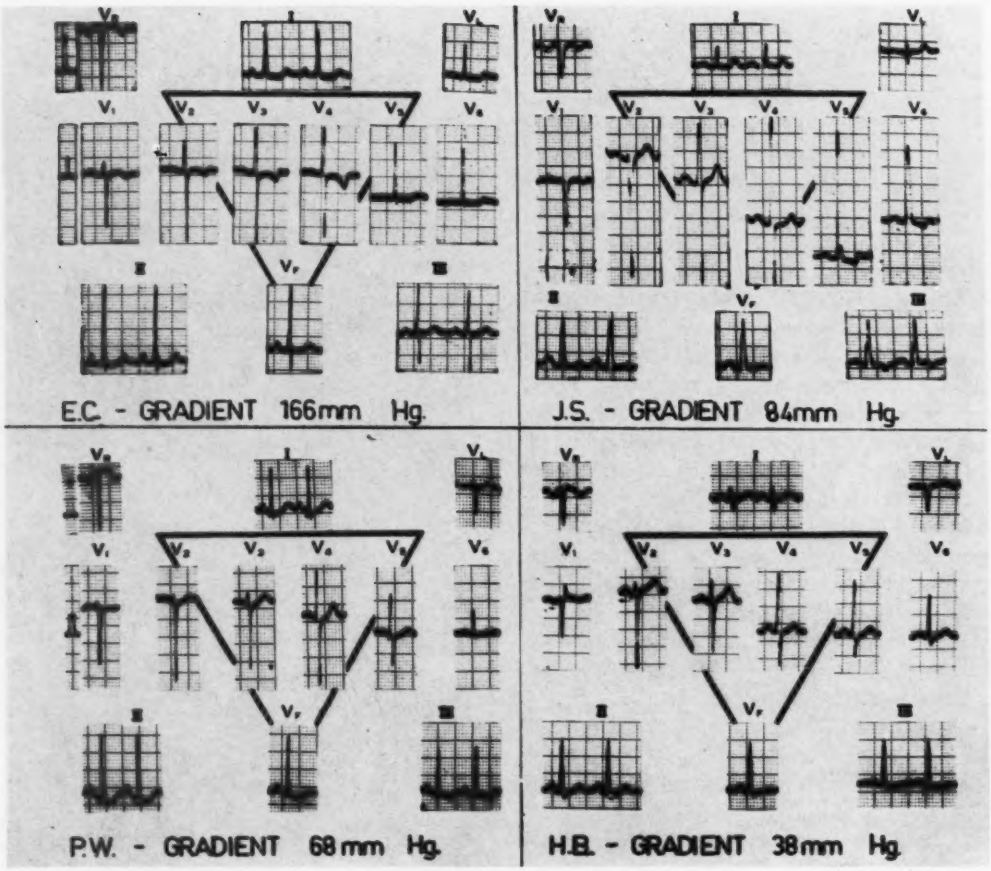

Figure 4

Electrocardiograms and systolic pressure gradients between left ventricle and high ascending aorta. The precordial leads in E.C. and P.W. have been recorded with half standardization.

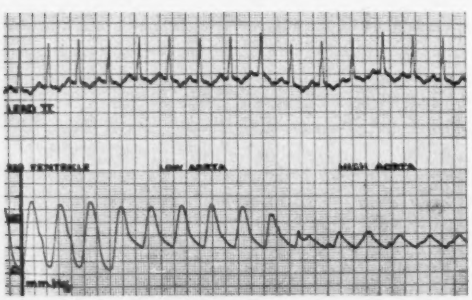

Figure 5

Pressure tracing in J.S. showing that the systolic gradient marking the site of stenosis lies above the aortic valve.

treatment for talipes, and she has recently undergone femoral herniorraphies. P.W. has retrognathism and both she and E.C. have incurving of the little finger on each hand. Abnormalities of physical development have been reported in other cases. Two patients have been considered to show some of the features of Marfan's syndrome. One of these, Denie and Verheugt's[1] patient, was of short stature but had long slender fingers and toes, prognathism, and a thoracic kyphosis. There was slight mucoid degeneration of the media of tne aorta at the site of the constriction and for a short distance along the coronary arter-

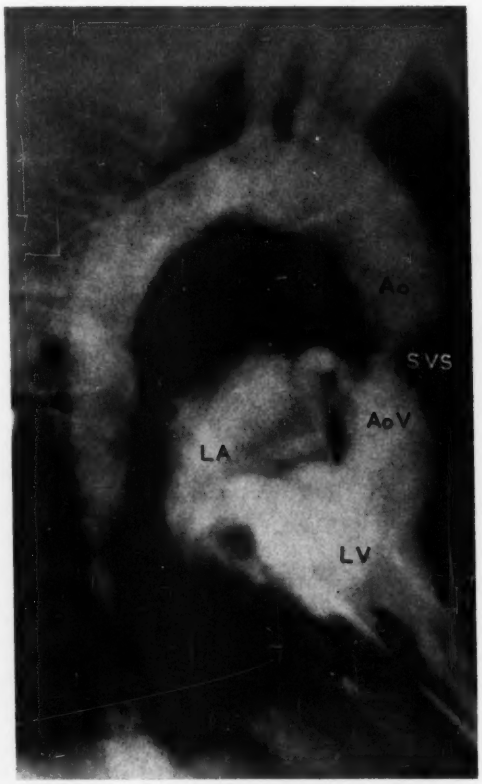

Figure 6 (Left)

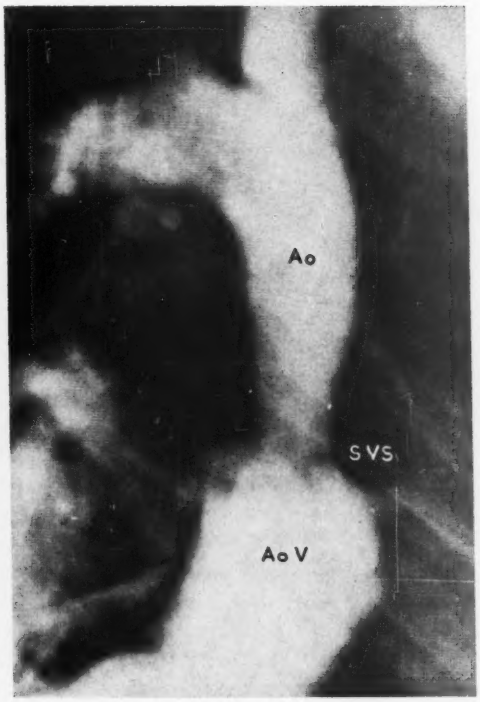

Figure 6 (Right)

Angiocardiograms in P.W. (Left) *and H.B.* (Right). *In each case the supravalvular aortic stenosis (SVS) is clearly shown above the aortic valve (A_oV).*

ies. The other, reported by Burry,[11] had long slender limbs, characteristic facies, high arched palate, and moderate kyphoscoliosis. Cystic medionecrosis of the aorta was not found at autopsy and features suggestive of Marfan's disease could not be found in the patient's relatives.

Subvalvular aortic stenosis appears to be commonly associated with other lesions of the aorta. Some degree of hypoplasia of the aorta distal to the stenosis (patient J.S.) has been a frequent finding.[1, 11, 14] A difference in blood pressure in the arms suggesting stenosis of the left subclavian artery was found in our patient E.C. and also in one of the cases described by Morrow and associates.[14] This latter patient had constriction of the aortic isthmus and Monckeberg-Gieben's patient[13] had coaretation of the aorta. In another case operation on a patent ductus arteriosus led to the discovery of supravalvular stenosis.[14] The aortic cusps have been tethered to the supravalvular stenosis in two cases,[1, 14] but in all reported cases the aortic valve has been tricuspid.

The degree of left ventricular hypertrophy, in the electrocardiograms of our patients correlates poorly with the systolic pressure gradient (fig. 4) but it is not known whether the cardiac indices were comparable when the gradients were recorded. In the patient J.S. the electrocardiographic abnormalities and the degree of cardiac enlargement in the chest roentgenogram seem more than what might reasonably be attributed to the measured left ventricular pressure load. This patient has a loud apical systolic murmur but neither the phonocardiogram nor the wedge pulmonary

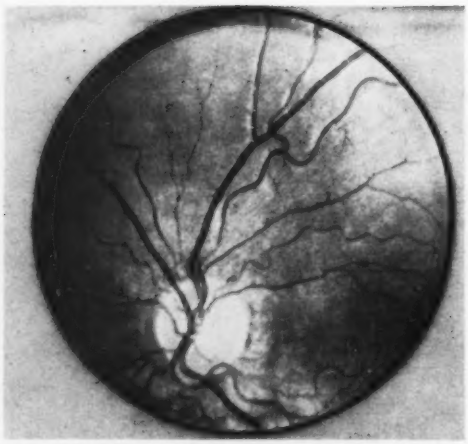

Figure 7

Fundal photograph of J.S. showing tortuosity of the retinal vessels.

artery pressure curve gave evidence of mitral incompetence so that the possibility of cardiomyopathy in addition to supravalvular aortic stenosis has been entertained. The left ventricular muscle in Denie and Verheugt's[1] patient was said to have shown an advanced stage of fibrous myocarditis, while in Burry's[11] case there were fibrosis of the endocardium and thinning of the myocardium toward the apex of the left ventricle, where the muscle fibers were atrophic and replaced by fibrous tissue. These patients were thought to be formes frustes of Marfan's syndrome, and diffuse fibrosis of the left ventricular muscle has been considered a likely contributory cause of cardiac failure in one instance of this condition.[20] On the other hand, taken together with the suspicion of a myocardial abnormality in our patient J.S., these reports raise the question whether myocardial degeneration may be another facet of a syndrome of supravalvular aortic stenosis in which the associated physical peculiarities are distinct from Marfan's disease.

The natural history of this uncommon condition is not known. In the patient H.B. serial electrocardiograms over 9 years show slowly progressive left ventricular hypertrophy. The earliest record of this patient, however, and an electrocardiogram of patient P.W. at 5 weeks (fig. 8), which was taken following the discovery of a cardiac murmur during a routine neonatal examination, both showed evidence of only right ventricular hypertrophy. Right ventricular hypertrophy in infancy has been reported in some cases of coarctation of the aorta and has been attributed to the effect on the neonatal circulation of a ductus arteriosus entering the aorta proximal rather than distal to the aortic constriction.[21, 22] Since aortic stenosis also may appear in infancy with electrocardiographic evidence of right ventricular hypertrophy,[23] it may be that conditions causing left ventricular systolic overload alter the fetal circulation, possibly by an increase in resistance to end-diastolic left ventricular filling or by septal hypertrophy, so as to lead to right ventricular hypertrophy.

Growth has been retarded in all our cases and the 28-year-old man described by Denie and Verheugt[1] was only 159 cm. tall and weighed 45.5 Kg. Limitation of exercise capacity by shortness of breath has not been reported in childhood but undue fatigue on effort has been a common early complaint. Dizziness on effort had been experienced by the 10-year-old girl J.R.[14] Denie and Verheugt's[1] patient was severely limited by angina and palpitation at the age of 25 years and the electrocardiogram had shown a progressive increase in left ventricular hypertrophy over the previous 6 years. The clinical course of this patient, however, may well have been affected by the presence of aortic incompetence and narrowing of the entry into the left sinus of Valsalva. Another patient died of cardiac arrest at the age of 10 years on the morning of projected operation.[14] Burry's[11] report of a patient dying at 37 years in congestive heart failure is the only other instance of natural termination of the condition.

In the supravalvular stenosis there is high pressure in the coronary arteries. It is possible that obstruction at this level may be better tolerated than obstruction at or below the aortic valve. Since myocardial oxygen consumption[24] and the tendency to left ven-

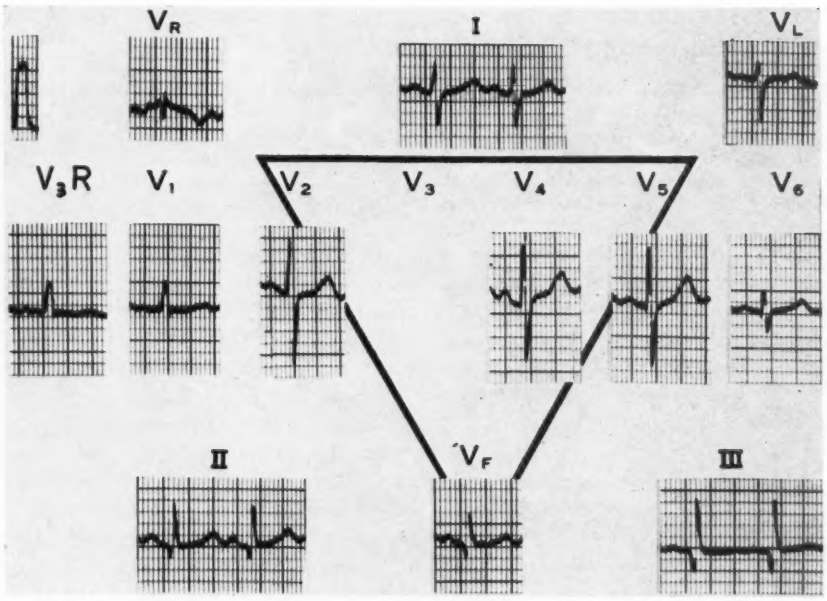

Figure 8

The electrocardiogram of P.W. at 5 weeks shows an upright T wave in V_1, an appearance suggesting the presence of right ventricular hypertrophy.[22]

tricular muscular hypertrophy may be expected to increase in direct proportion to the systolic pressure load, it appears reasonable to adopt criteria for surgical relief similar to those applied to the more common forms of aortic stenosis. At operation on our two patients with the higher systolic gradients (E.C., J.S.) the insertion of a Teflon patch into the aortic wall at the site of the constriction effectively relieved the supravalvular stenosis as judged by abolition of the pressure gradient. Although the long-term result of this type of operation is not yet known, it is encouraging that a year after operation the electrocardiogram in the patient with the longer follow-up shows changes suggesting a significant reduction in left ventricular hypertrophy.

Summary

Facial resemblance to a patient in whom supravalvular aortic stenosis was discovered and successfully relieved at operation has led to the correct diagnosis of supravalvular stenosis in three other patients. All four patients are mentally subnormal. The presence of supravalvular aortic stenosis in mentally retarded patients with the unusual facial features here detailed may constitute a syndrome that has not previously been described.

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Cardiac Hypertrophy

There are many cases of hypertrophy, and of great hypertrophy of the heart, in which during life and after death no source of increased work can be discovered. The degree of enlargement found in many hearts in which there is a valve defect, such as aortic regurgitation or mitral stenosis, is sometimes out of all proportion to the apparent increase of burden. There is still much that remains to be explained; it is clear that there must be hidden sources of increased work, or the conclusion that increased work is the cause of hypertrophy needs revision.—SIR THOMAS LEWIS. *Diseases of the Heart.* New York, The MacMillan Company, 1933, p. 106.

Experiments in India on "Voluntary" Control of the Heart and Pulse

By M. A. WENGER, PH.D., B. K. BAGCHI, PH.D., AND B. K. ANAND, M.D.

PROMINENT among the many claims of unusual bodily control that emanate from practitioners of Yoga is the ability to stop the heart and radial pulse. Such claims often have been authenticated by physicians, and one "experiment" employed a loud-speaker system so that a large crowd could hear the heart sounds before and after their disappearance. To our knowledge, however, only one investigator had published electrocardiographic results before the work now reported.

In 1935 a French cardiologist, Dr. Thérèse Brosse, took portable apparatus to India and obtained measurements from at least one person who claimed the ability to stop the heart. A published excerpt from her data[4] involving one electrocardiographic lead, a pneumogram, and a pulse wave recording from the radial artery, shows the heart potentials and pulse wave decreasing in magnitude approximately to zero, where they stayed for several seconds before they returned to their normal magnitude. The data were held to support the claim that the heart was voluntarily controlled to a point of approximate cessation of contraction.

During our investigations in India we searched for persons who claimed to stop the heart or pulse, and were cordially assisted by many individuals including the Indian press. We found four. Another claimed only to slow the heart. Of the four, only three consented to serve as subjects, and one of these claimed he was too old to demonstrate heart stopping without a month or so of preparatory practice. Since he was the subject studied by Dr. Brosse in 1935 we were particularly anxious to gain his cooperation and, after considerable persuasion, he consented to demonstrate for us the method he had employed in "stopping the heart" for Dr. Brosse.

From the University of California, Los Angeles; The Medical School, University of Michigan, Ann Arbor; and the All India Institute of Medical Sciences, New Delhi.

This work was made possible by grants from the Rockefeller Foundation, The Rackham Foundation of the University of Michigan, and subcontract AF 18 (600)-1180 from George Washington University, and was sponsored by the Indian Council of Medical Research. Individual acknowledgments have been recorded elsewhere.[1-3] The analysis of the data was supported, in part, by research grant M-788 from the Institute of Mental Health, National Institutes of Health, U. S. Public Health Service.

Apparatus and Procedures

Our apparatus has been described elsewhere.[1-3] Briefly, it consisted of an 8-channel Offner type-T portable electroencephalograph with appropriate detectors and bridges for DC recording of respiration, skin temperature, electrical skin conductance, and finger blood volume changes. Procedures varied according to the cooperativeness of the subject and other circumstances. For that reason the results are reported for individual subjects.

Results

The first two subjects claimed they could stop the heart. No. 1. Shri Sal Gram, at Yogashram, New Delhi, made four attempts at one session. Only one electrocardiographic lead (III) and respiration were recorded, in what was planned as a preliminary experiment. The subject stood in a semi-crouched posture with the left side pressed against a table. Under retained deep inspiration considerable muscular tension was apparent in neck, chest, abdomen, and arms. Stethoscopically detected heart sounds either disappeared briefly or were obscured by sounds from muscle action. Palpable right radial pulse weakened or disappeared briefly at each attempt to stop the heart. Electrocardiographic records were replete with muscular artifacts but were readable for rate and QRS potential changes. Little change occurred in magnitude of potentials; changes in heart rate were small. There was no indication of heart arrest. The subject refused further cooperation.

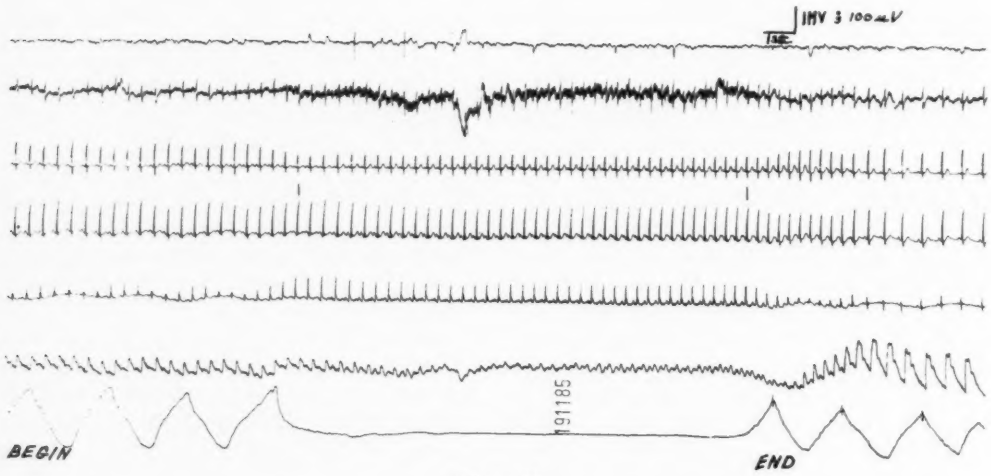

Figure 1

One "heart stopping" attempt by Shri Ramananda Yogi. The channels and variables are (1) muscle potentials, right biceps; (2) muscle potentials, right abdominus rectus; (3) electrocardiographic lead I; (4) electrocardiographic lead II; (5) electrocardiographic lead III; (6) plethysmograph, left index finger; (7) respiration. Calibration was 100 μv/cm. for the electromyogram and 1 mv/cm. for the electrocardiogram. Chart speed was 1.25 cm./sec.

No. 2. Shri Ramananda Yogi, of Andhra, age 33, at All India Institute of Medical Sciences, New Delhi, made seven attempts on 2 days, and additional experiments on a third day during fluoroscopy and x-ray photography,* all in a supine position. This work was initiated in the laboratory of the third author who became interested in the results and was asked to collaborate. His account of the second and third days of experimentation follows:

I examined Shri Ramananda Yogi on March 7, 1957, during two experiments in which he claimed he could stop the heart and pulse. He was investigated during these experiments electroencephalographically and electrocardiographically by Drs. Wenger and Bagchi, who also recorded his finger blood volume, respiration, blood pressure, and muscular activity. In the first experiment, Shri Ramananda Yogi stopped his respiration after taking four deep breaths. The breath was held in inspiration with closed glottis and the chest and abdominal muscles were strongly contracted. By this maneuver the pressure in the thorax was raised. During this period I could feel a very feeble pulse which had a normal rate in the beginning but became quick in the later part of the experiment. The heart sounds could not be heard but one could hear faint murmurish sounds due to the contraction of the thoracic muscles. The neck veins became distended. The breath was held for 15 seconds. This was immediately followed by quickening of the respiration, quick and deep pulse, and loud heart sounds. After a few seconds the heart rate returned to normal. The resting blood pressure had been 130/96 mm. Hg. Immediately following the breath holding it was raised to 210/100.

During the breath-holding period when the pulse was almost imperceptible and no heart sounds could be heard, the electrocardiograph continued to show contractions of the heart. The electrocardiographic pattern showed a slight right axis deviation which disappeared when respiration started again.

In the next experiment, he repeated the same procedure but held the breath in expiration. All other maneuvers were the same. The pulse, although very feeble, could still be felt. No heart sounds could be heard. Venous congestion in the neck took place. The electrocardiograph showed that the heart contractions continued but this time

*The radiologic investigations were conducted at Irwin Hospital with the assistance of Dr. N. G. Gadekar. The authors are grateful to him for his collaboration.

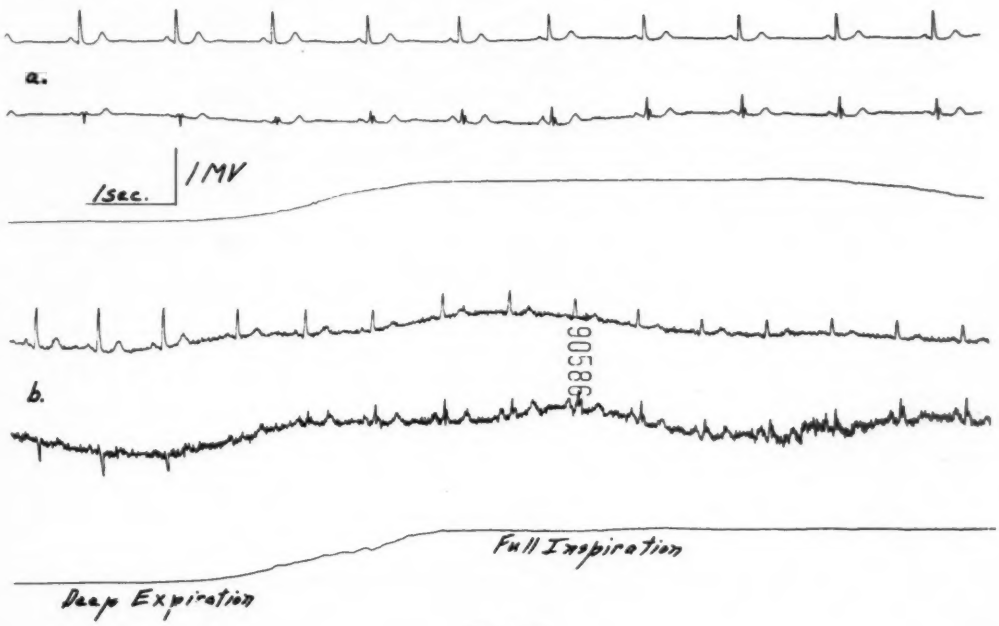

Figure 2

From demonstration by Shri Krishnamacharya of method used in "heart stopping." Electrocardiographic leads I and III, and respiration, are shown in that order (a) at rest, and (b) during demonstration. Calibration was 1 mv./1.5 cm. Chart speed was 2.5 cm./sec.

there was a slight left axis deviation. All other responses were similar to those in the first experiment.

Next day Shri Ramananda Yogi had skiagrams of the chest taken before experimentation and during two experiments, again attempting to stop the heart and pulse, one holding the breath in inspiration, and the other holding the breath in expiration. In both experiments one finds that the maximum transverse measurement of the heart decreases. Normally the maximum transverse measurement was 12 cm. During the first experiment (inspiration) it was decreased to 11 cm. During the second experiment (expiration) it was decreased to 11.5 cm.

Figure 1 shows the first attempt of March 7. During maintained inspiration the QRS potential is seen to decrease in lead I and to increase in lead III. (In the second attempt, during maintained expiration, the potentials increased in lead I and decreased in lead III.) The first two channels show muscle action potentials from the right biceps and the right abdominus rectus at the level of the umbilicus. Marked increases are seen to have occurred in the abdominal recording only. The plethysmographic recording shows that the finger pulse was always detectable, and that the pulse volume was greatly increased immediately after termination of the attempt. No unusual changes were detected in the electroencephalographic records.*

No. 3. Shri T. Krishnamacharya, of Madras, age 67, at Vivekananda College, Madras. This gentleman was the one who had "stopped his heart" for Dr. Brosse in 1935 but would not repeat the attempt for us. He finally consented to demonstrate the method he had employed, but with minimum apparatus attached: a blood pressure cuff, electrocardiographic leads I, II, and III, and a respiration

*This subject had engaged in a number of pit-burial demonstrations but refused us cooperation in that respect. Recently, however, he has cooperated with the third author and Dr. Gulzar Singh in such work. The results are to be reported soon.

Table 1

Variability in Heart Period in Last Phase of Heart Slowing Experiments of Subject no. 4 (HP in seconds)

Experiment no.	1	2	3*	1	2	1	2
Date		4/25			5/23		5/24
Initial range		0.6-0.9			0.7-0.8		0.7-0.9
Last 10	1.2	1.2	0.7	1.8	1.3	1.9	1.7
heart periods	1.1	1.6	0.8	1.8	2.1	1.8	2.0
	1.4	1.4	0.9	1.8	*2.5*	1.9	1.9
	2.6	2.0	0.9	*2.8*	2.0	1.9	1.9
	2.5	1.6	1.2	1.9	1.8	1.9	1.8
	1.9	*2.9*	1.6	2.2	2.4	1.8	1.8
	2.3	2.2	1.8	2.1	2.0	1.8	1.8
	2.1	2.3	*2.0*	2.0	2.2	1.6	1.8
	2.0	2.1	1.7	2.0	2.1	1.6	1.8
	1.7	1.6	0.9	1.8	1.4	1.5	1.3
Just after maneuver	0.8	0.9	0.6	1.2	0.9	1.2	0.7
Longest HP	2.6	2.9	2.0	2.8	2.5	2.8	2.9

**Uddiyana* alone

belt; none of which he would tolerate fastened tightly. He said his radial pulse might stop, but his heart wouldn't. The method proved to be similar to that employed by Shri Ramananda Yogi during maintained inspiration. The muscular effort expended was less, but the periods of maintained inspiration were considerably longer. Again, the blood pressure increased, the maximum change being from 128/80 to 140/105. There were no definite "attempt" periods for this subject. He merely permitted us to record data while he reclined and engaged in *pranayama* (breath control) as he pleased. On three attempts to measure blood pressure no sounds could be heard from the brachial artery. On another day with the subject seated, a physician was permitted to palpate both radial arteries and listen to heart sounds stethoscopically.† He reported no absence of heart sounds but at one time the radial pulse was not detectable in either wrist.

We believe the most significant data from these experiments are the changes in QRS potentials in leads I and III (fig. 2). As we previously had found with Shri Ramananda Yogi, during maintained inspiration with glottis closed and with increased tension in abdominal muscles, the heart potentials decreased in lead I but increased in lead III. Again, right axis deviation of the heart is indicated.

No. 4. Shri N. R. Upadhyaya, age 37, at Kaivalyadhama, Lonavla. This gentleman did not claim to stop the heart. He claimed only to slow it. He was a student of Yoga with more than 5 years of training, and had discovered accidentally that he could slow his heart. The maneuver occurred in the reclining position and during maintained inspiration. Just before the attempt a rolled towel was inserted under the lumbar area of the spine which gave a support 4 or 5 inches in height. After inspiration the subject engaged in the Yogic posture known as *uddiyana*, which involves a raising of the diaphragm and an inward distention of the abdomen, and accompanied it with another posture known as *jalandabar bandha*, in which the chin is depressed and extended toward the chest.

We tested him on 3 days, and on the first 2 days applied electrocardiographic chest leads V_2 and V_5 in addition to standard leads I, II, and III. There were only small changes in the magnitude of the QRS potential in any

†The authors are indebted to Dr. S. T. Narasimhan of Madras for his assistance in this experiment and for his genial aid in our work.

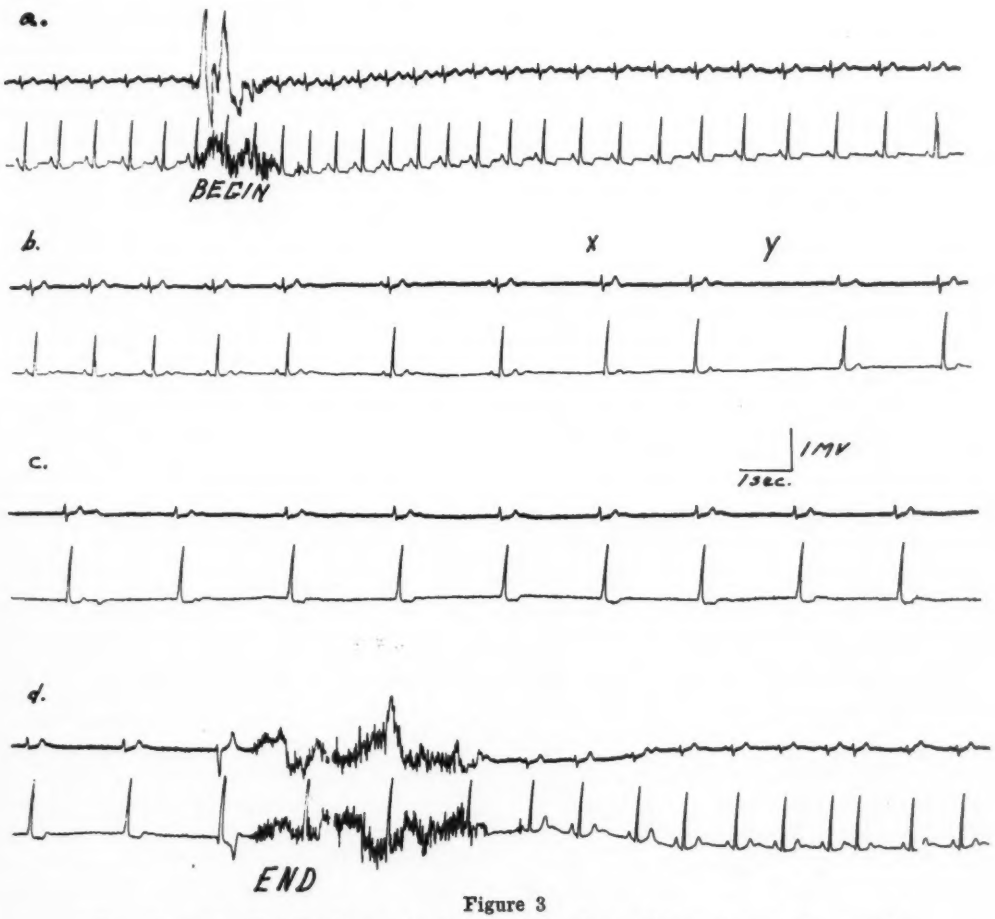

Figure 3

One attempt by Shri Upadhyaya to slow the heart. Sequential portions of the recording of electrocardiographic leads I and III are shown. Calibration was 1 mv/cm. Chart speed was 1.25 cm./sec. The P wave disappeared (x) and was absent for 16 heart cycles. The longest cycle length (Y) was almost 3 seconds.

lead. There was, however, a marked slowing of the heart in each test. In addition to bradycardia we found an increase in the P-R interval and finally a marked decrease or disappearance of the P wave. Thus a nodal rhythm appeared for a few beats before the subject terminated the maneuver. Figure 3 demonstrates the longest P-wave depression we obtained. The longest cycle length was approximately 3 seconds.

Our attempts to discover the mechanisms contributing to these results were not fruitful. Pressure on the carotid sinuses produced an increase rather than a decrease in heart rate. The chin lock alone (*jalandabar bandha*) produced little or no change. *Uddiyana* alone produced some bradycardia and one cycle of almost 2 seconds' duration, as may be seen in the third column of table 1. The other columns of the table show (a) the durations of the last 10 cycle lengths in the six main experiments, (b) the premaneuver range, (c) the first postmaneuver heart period, and (c) the longest recorded heart period. The period-to-

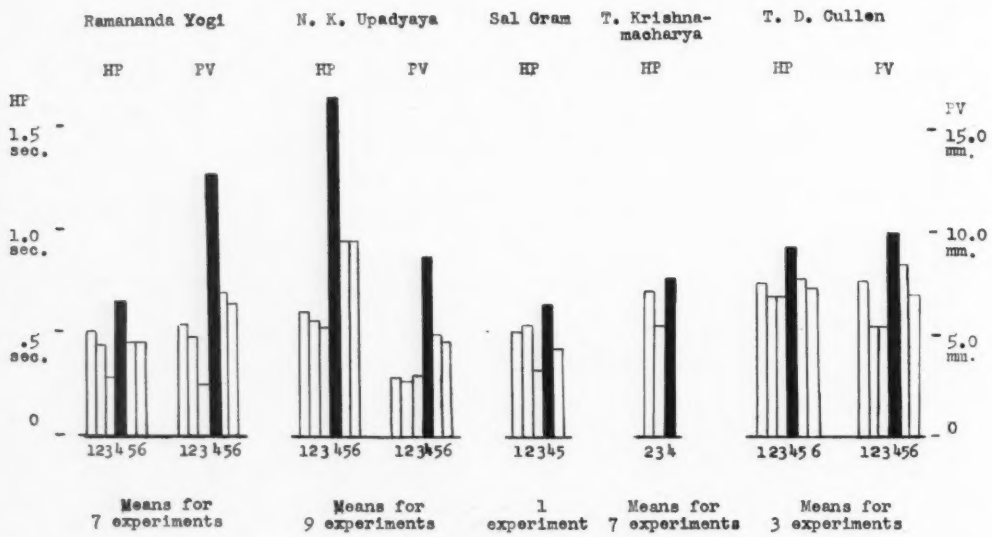

Figure 4

Summary of experiments on control of the heart. Each entry for heart period (HP) and finger pulse volume (PV) represents pooled means for samples of 10 heart cycles from each phase of each experiment. Different phases of the experiments are indicated as follows: 1. Initial rest. 2. After instructions. 3. Fastest HR and lowest PV during maneuver. 4. slowest HR and highest PV during and just after maneuver. 5. 50 HP after sample no. 4. 6. 100 HP after sample no. 4.

period variability is apparent. Of additional interest is the observation that only on the last day of experimentation was the maneuver maintained for 10 or more heart cycles beyond the greatest bradycardia. Apparently experience or amount of attached apparatus, or both, influence the effects of this maneuver. This subject is still available for research. Subsequent work by Indian investigators supports the above observation in that a heart period of 5.6 seconds has now been recorded.[5] Perhaps they will discover the mechanisms underlying the effect.

Discussion

It is obvious that the subjects we tested do not voluntarily control the heart muscle directly. In each instance some striated muscle action intervenes. Through muscular and respiratory control certain changes do occur in circulatory variables. Figure 4 shows changes in heart period and (for some subjects) finger pulse volume for the Indian subjects and for one American (Dr. Cullen)* who attempted to repeat the Valsalva experiment. Decreased heart rate was greatest in the subject who claimed only to slow the heart. The greatest changes in finger pulse volume occurred in Shri Ramananda, who exerted utmost effort to demonstrate "heart stopping." Dr. Cullen employed less effort, although his pattern for heart period is not greatly different from that of Shri Ramananda.

For the first three subjects we assume that by increased tension in the muscles of the abdomen and thorax, and with closure of the glottis, there is developed an increased intrathoracic pressure that interferes *with the venous return to the heart.* With little blood to pump the heart, sounds are diminished, as

*The authors are indebted to Dr. Thomas Cullen, University of California, Los Angeles, for his participation in this experiment and for his assistance in analyzing the data.

well as being masked by muscular sounds, and the palpable radial pulse seems to disappear. High amplification finger plethysmography continues to show pulse waves, however; and the electrocardiograph shows that the heart goes on contracting. The electrocardiograph also shows right axis deviation under deep inspiration. The QRS potentials in lead I are markedly decreased. It seems, therefore, that Dr. Brosse's record of "heart control" is to be so explained. She recorded lead I only from Shri Krishnamacharya. Had she recorded lead III, or had she recalled the results of the Valsalva maneuver, she probably would not have claimed that her subject voluntarily controlled his heart.

It is of interest to know that our conclusions have had a forerunner in India. After completion of our work we discovered a monograph published in 1927 by Dr. V. G. Rele of Bombay.[6] Although he published no data, he writes of electrocardiographic records and x-rays on one subject, and reached conclusions similar to ours, although he extended them more than we care to do.

Our fourth subject demonstrated a different phenomenon that further research may explain. It could be said that he "stopped the heart" for a few seconds. We prefer to assume that by some striated muscular mechanism he stimulated the vagus output to the sinoatrial node, interrupted it, and thus interrupted regular cardiac cycles and a nodal rhythm was briefly established.

In this connection a recent publication in California is of interest.[7] A patient complained of heart slowing when he relaxed. Published electrocardiograms show a period of standstill of approximately 5 seconds followed by a QRS potential with no P component. The report, supplemented by private correspondence, indicates that there were no changes in QRS magnitude but that the P wave at the end of the periods of bradycardia was reduced or absent. Contrary to our Indian subject, he apparently employed no intervening muscular or respiratory mechanism. He merely relaxed. His data call to mind other examples of voluntary control over supposedly involuntary musculature, such as one reported by Lindsley and Sassman[8] with pilomotor control, and one[2] with sudomotor control. Such examples probably are to be explained in terms of accidental conditioning.

Summary and Conclusions

Among other studies in India the authors investigated four practitioners of Yoga in respect to control of the heart and pulse. Two claimed to stop the heart. One formerly made this claim but only demonstrated his method. The fourth claimed only to slow the heart.

The method for the first three was similar, involving retention of breath and considerable muscular tension in the abdomen and thorax, with closed glottis. It was concluded that venous return to the heart was retarded but that the heart was not stopped, although heart and radial pulse sounds weakened or disappeared.

The fourth subject, with different intervening mechanisms also presumably under striated muscle control, did markedly slow his heart. The data indicate strong increase in vagal tone of unknown origin.

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The Effects of Angiotensin on Pulmonary Circulation and Ventricular Function

By Paul N. Yu, M.D., Milton N. Luria, M.D., James K. Finlayson, M.B., C. Alpheus Stanfield, M.D., Herbert Constantine, M.D., and F. Joseph Flatley, M.D.

ALTHOUGH the discovery of angiotensin (angiotonin or hypertensin) was reported independently in 1939 by Page and Helmer[1] in this country and by Braun-Menendez and co-workers[2] in Argentina, its structure was not described until 1956 and its active principle not synthesized until 1957. Angiotensin is known to exist in at least two forms, angiotensin I and angiotensin II. While the decapeptide angiotensin I does not have vasoconstrictor properties, the octapeptide, angiotensin II, formed by action of the converting enzyme on angiotensin I, is an extremely powerful vasoconstricting agent.[3, 4]

Circulatory effects of synthetic angiotensin in animals have been extensively studied by Page and his associates and other investigators.[5-7] Many workers have reported the hemodynamic effects of various angiotensin preparations in normotensive subjects.[8-14] However, there has been scanty information in the literature regarding the effects of angiotensin on pulmonary circulation and ventricular function in man. It is the purpose of this paper to report these effects of angiotensin II in 16 normotensive patients. Data of hemodynamic studies in eight anesthetized dogs were also included for delineation of some of the findings in human studies.*

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Clinical Material and Method

Human Studies

Sixteen patients with normal systemic and pulmonary artery pressures were studied. There were 11 males and five females whose ages ranged from 17 to 60 years. None of these patients had clinical or physiologic evidence of aortic stenosis, mitral valvular disease, or intracardiac shunts.

Right heart catheterization was performed in the usual manner. The methods of determining the cardiac output and recording blood pressures have been previously reported in detail,[16] and the technic of inscribing indicator-dilution curves and measuring the total and "central" blood volumes has also been described elsewhere.[17] The cardiac output determined by the dilution curves was used for the calculation of "central" blood volume. The indicators (iodinated I^{131} human serum albumin or Indocyanine Green, or both) were injected into the main pulmonary artery and the dilution curves recorded from the femoral artery. The pressures were measured by Statham transducers and carrier amplifier connected to a Sanborn Polyviso Cardiette, and the mean pressures were obtained by electrical integration.

The formulas used to derive resistances and ventricular work against pressures were modified from the paper by Gorlin and Gorlin.[18] Mean pulmonary wedge (considered as left ventricular end-diastolic) and right ventricular end-diastolic pressures were used respectively in the calculation of left and right ventricular work against pressure. The cardiac output determined by the Fick procedure was used for the calculation of vascular resistance and ventricular work against pressure. In patients with aortic insufficiency the calculated left ventricular work against pressure would be less than the actual value.

When the patient's condition was stable, pres-

*Since we completed our studies, Page and Bumpus have published an excellent review on angiotensin.[15]

sures were recorded from the right atrium and right ventricle. Subsequently, measurements of cardiac output (both by the Fick procedure and indicator-dilution curves) and of femoral arterial, pulmonary arterial, and pulmonary wedge pressures were made.

Angiotensin* diluted in 5 per cent dextrose in water was injected through an antecubital vein at the rate of 0.015 to 0.135 microgram per kilogram of body weight per minute, depending upon the rise of the systemic blood pressure, which was monitored continuously by direct intra-arterial recording. During infusion one or more cardiac output determinations were made, followed immediately by recording femoral arterial, pulmonary arterial, and pulmonary wedge pressures, and sometimes by measurement of right ventricular and right atrial pressures.

Animal Studies

Eight adult mongrel dogs were kept lightly anesthetized by separate small injections of intravenous thiopental. With chest open and intermittent positive pressure respiration, a cardiac catheter was introduced into each of the following sites: (a) right atrium or right ventricle, (b) main pulmonary artery, (c) pulmonary wedge position, (d) pulmonary veins, and (e) left atrium. Following the insertion of various catheters, which were securely anchored with stay sutures, the chest was tightly closed and spontaneous respiration started.

A polyethylene tube was then introduced into the abdominal aorta via a femoral artery for arterial blood sampling and pressure recording. The position of the cardiac catheters was frequently checked by pressure recordings.

Cardiac output in the dogs was determined by indicator-dilution curves by use of the dye Indocyanine Green. After each determination of the cardiac output, the blood drawn in a syringe mounted on the Colson Constant-Flow System was reinfused into the dogs, so that the blood loss was kept minimal.

Intracardiac and intravascular pressures were measured in the same manner as that described in human studies. In most instances, pulmonary arterial and right ventricular pressures were recorded alternately on the same channel. The formula for calculating left ventricular stroke work was similar to that employed in human studies except that the left atrial mean pressure was substituted for the left ventricular diastolic pressure.

In a series of five dogs, following control studies, a rapid infusion of heparinized blood was given through a cardiac catheter into the right side of the heart by means of a reservoir. Similar to the experimental studies designed by Sarnoff and Berglund,[19] the amount of blood infused and the pressures in both atria could be varied over wide ranges by changing height of the reservoir. The initial amount of blood infused was about 15 ml./Kg. and increased to approximately 60 ml./Kg. in different stages. Studies were repeated within 5 minutes of the completion of each infusion. After the effects of rapid infusion of known volume of blood had been studied, a "phlebotomy" to remove rapidly slightly less than the total volume of blood infused was accomplished by simply lowering the reservoir. When the circulatory state had stabilized, pressure and flow measurements were again made and the figures used as the second control values. Subsequently, angiotensin (1 to 2 μg./Kg./min.) was infused into an external jugular vein. During the administration of angiotensin solution, rapid blood infusion was again given in

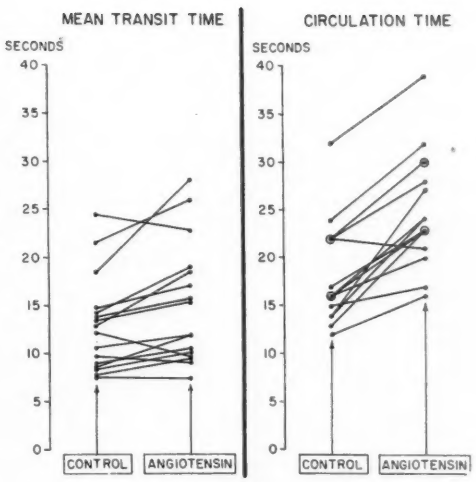

Figure 1

The left panel shows changes in the mean transit time from the pulmonary artery to the femoral artery, and the right panel shows the changes in the circulation time as represented by the interval between the peak of primary circulation and that of recirculation of indicator-dilution curves in a series of normotensive patients. Note that there was more striking prolongation of the circulation time than of the mean transit time. Thus, the slower circulation occurred mainly in the systemic circuit and not in the pulmonary circuit and left heart.

*Hypertensin II (CIBA), Courtesy of Dr. William E. Wagner, CIBA Pharmaceutical Products, Inc., Summit, New Jersey.

Table 1

Effects of Angiotensin on Rate of Blood Flow and Blood Volume

Parameters	No. of subjects	Average during control period (A)	Average during angiotensin infusion (B)	Average difference (B-A) ± SE	p Value
Fick procedure					
$\dot{V}_{O_2}$ (ml./M.²/min.)	16	138.5	147.8	9.3 ± 3.3	< 0.01
Ca_{O_2}—$C\bar{v}_{O_2}$ (ml./L.)	16	38.9	49.5	10.6 ± 4.4	< 0.05
CI (L./M.²/min.)	15	3.80	3.26	−0.54 ± 0.24	NS
HR (beats/min.)	16	85	76	−9 ± 4.7	NS
SI	15	45	46	1 ± 2.8	NS
Indicator-dilution curve					
CI (L./M.²/min.)	16	3.80	3.40	−.40 ± 0.24	NS
T_M (sec.)	16	13.2	15.3	2.1 ± 0.74	$0.01 < p < 0.02$
T_E (sec.)	16	18.3	25.0	6.7 ± 0.83	< 0.01
"CBV" (ml./M.²)	16	789	801	12 ± 10.1	
TBV (ml./M.²)	12	2800	2795	−5 ± 27.8	NS

$\dot{V}_{O_2}$, oxygen consumption; $Ca_{O_2} - C\bar{v}_{O_2}$, arteriovenous difference; CI, cardiac index; HR, heart rate; SI, stroke index; T_M, mean transit time from pulmonary artery to femoral artery; T_E, circulation time from femoral artery to femoral artery; "CBV", "central" blood volume or dilution volume from pulmonary artery to femoral artery; TBV, total blood volume; SE, standard error of mean; p indicates the probability that difference as large as that observed will occur by chance—a difference with a chance probability of 0.05 or less is considered to be significant; NS, not significant.

the same manner as previously described. Determination of cardiac output and measurements of pressures were carried out repeatedly during angiotensin infusion with or without rapid blood infusion. Table 3 shows the values of various parameters in a given dog by averaging two or more determinations obtained during a certain circulatory state, (i.e., blood or angiotensin infusion).

In another three dogs pressure and flow measurements were first made during a control period as well as during angiotensin infusion, with graded doses ranging from 0.1 μg./Kg./min. to 5 μg./Kg./min. In two of these dogs, after angiotensin infusion was discontinued, single or multiple doses of hexamethonium (5 to 10 mg.) were given intravenously to lower the systemic arterial pressure. When the systolic pressure reached a level slightly less than 50 mm. Hg the angiotensin infusion was recommenced. In each case systemic and pulmonary arterial pressures were again recorded.

Results

Human Studies

The results are summarized in tables 1 and 2.

During angiotensin infusion there were statistically significant increases in femoral arterial, pulmonary wedge, and pulmonary arterial pressures. No statistically significant change was observed in cardiac output, heart rate, and stroke volume. For the whole group, there was a parallel increase in oxygen consumption and in the arteriovenous oxygen difference. However, significant increase in oxygen consumption, i.e., more than 13 per cent of the control value, was noted in only six patients. The cause of this increase was not apparent.

Total systemic, total pulmonary, and pulmonary vascular resistances and the left ventricular work against pressure were all statistically increased. In most cases, however, the magnitude of increase in the pulmonary vascular resistance was small.

In seven patients in whom right ventricular pressure was measured, there was a consistent rise in both systolic and diastolic pressures directly proportional to the magnitude of elevation of pulmonary artery pressure. In six of these seven patients the right ventricular work against pressure was also increased.

In most instances there was a slight prolongation in the mean transit time from the pul-

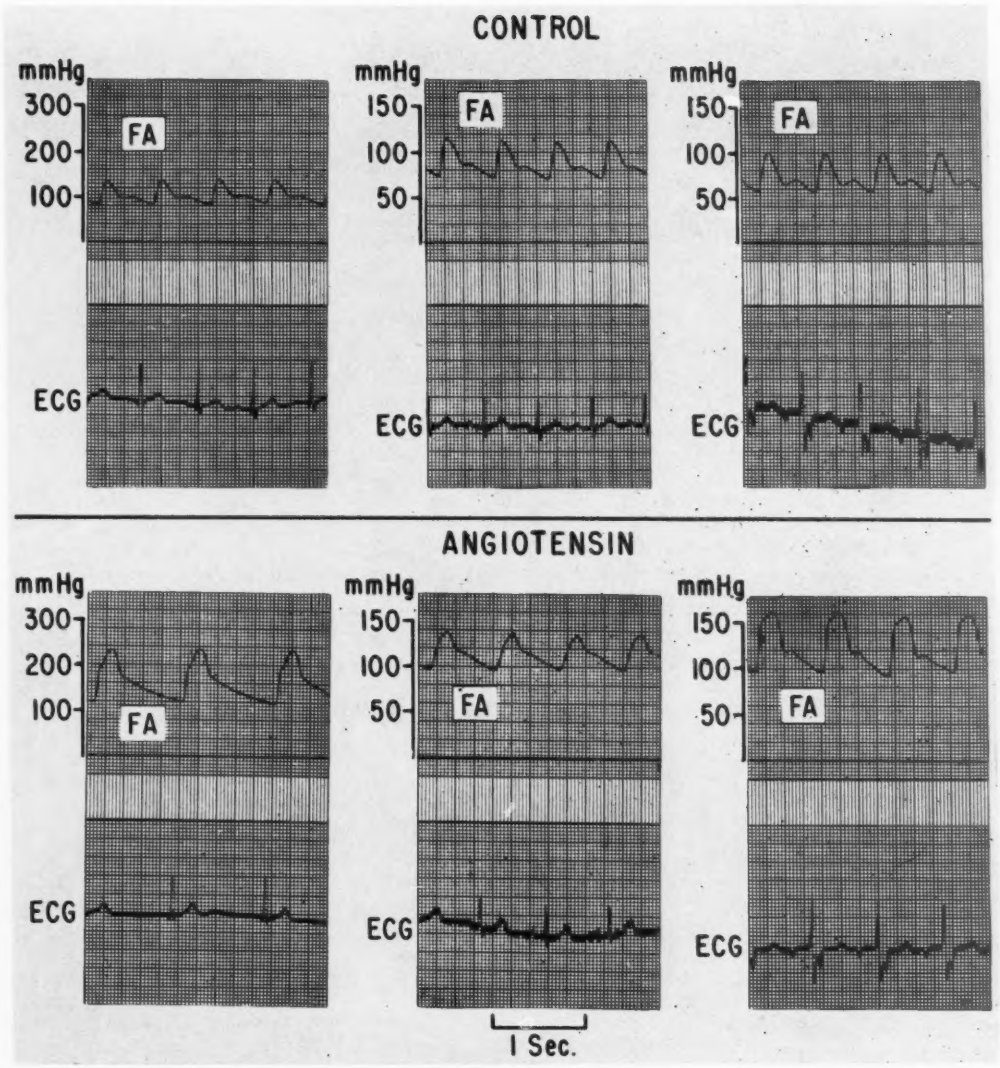

Figure 2

Femoral arterial pressure tracings recorded during the control period (upper half) and during angiotensin infusion (lower half) in three patients. Note the prolongation of the upstroke time and the appearance of an anacrotic notch.

monary artery to the femoral artery, although the total and "central" blood volumes and arterial oxygen saturation usually remained unchanged. In all but one case there was a prolongation in the circulation time as measured by intervals between the peak of primary circulation and that of recirculation of indicator-dilution curves (fig. 1).

The increase in the femoral arterial, pulmonary wedge, and pulmonary arterial pressures usually occurred within 2 minutes of the start of intravenous injection of angiotensin and

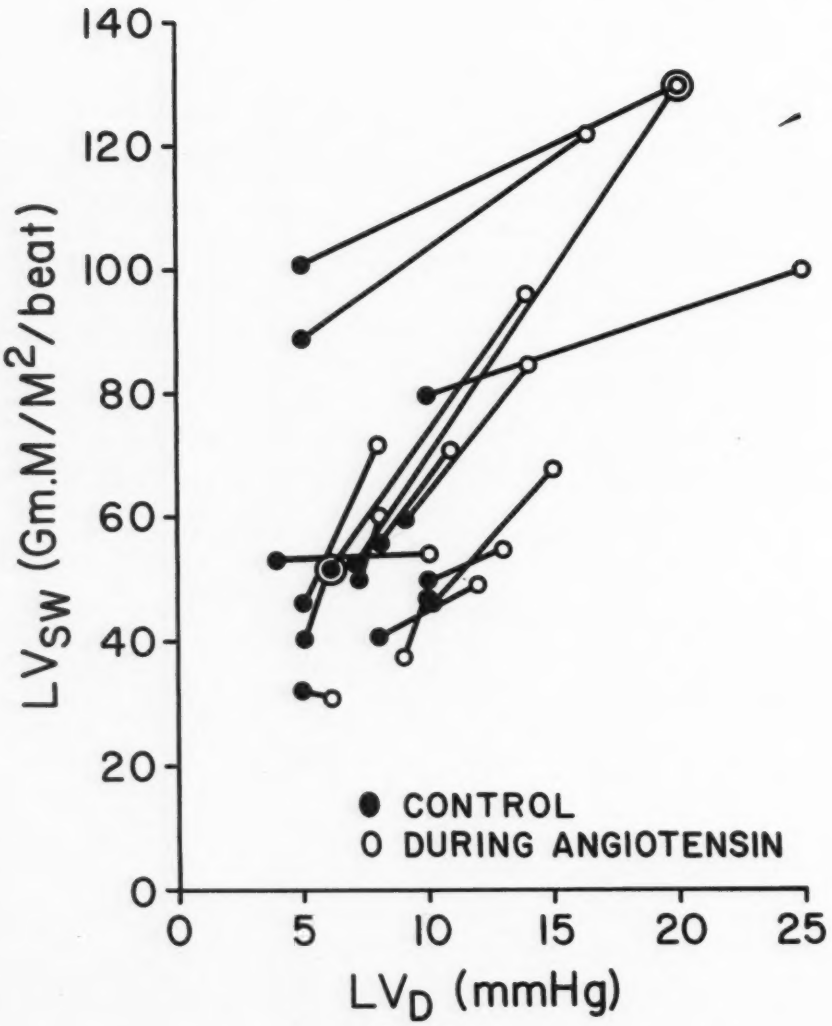

Figure 3

During angiotensin infusion a positive correlation was observed between the increment in the left ventricular work against pressure and that in the left ventricular diastolic pressure (as represented by the mean pulmonary wedge pressure) in all but two patients (E. H. and G. P).

reached its maximum within 5 minutes of infusion.

During angiotensin infusion in nine of the 16 patients there was a significant increase in the upstroke time of the femoral arterial pressure tracing associated with the presence of an anacrotic notch close to the top (fig. 2). In the remaining seven patients no such change in the contour of femoral arterial pressure tracings was observed. There was no alteration in the pressure distribution through the cardiac cycle.

In some cases a graded increase in the dose of angiotensin produced further elevation of

Table 2

Effects of Angiotensin on Systemic and Pulmonary Blood Pressures and Resistances and Ventricular Work

Parameters	No. of subjects	Average during control period (A)	Average during angiotensin infusion (B)	Average difference (B-A) ± SE	p Value
Blood pressures (mm. Hg)					
FA					
S/D	16	123/67	166/92	—	—
Mean	16	87	119	32 ± 4.6	< 0.001
RV	7	23/4	36/8	—	—
PA					
S/D	16	22/8	33/13	—	—
Mean	16	12	20	8 ± 1.8	< 0.001
"PC"$_m$	16	7	13	6 ± 1.3	< 0.01
Resistances (dynes-sec/cm.^{5})					
TSR	15	1155	1916	761 ± 154	< 0.001
TPR	15	161	312	151 ± 22	< 0.001
PVR	15	73	127	54 ± 14.6	< 0.01
Stroke work against pressure (Gm.M/beat/M.^{2})					
LV	15	56	76	20 ± 5.3	< 0.001
RV	7	8	15	—	—

FA, femoral artery; S/D, systolic/diastolic; RV, right ventricle; PA, pulmonary artery; "PC"$_m$, pulmonary wedge; TSR, total systemic; TPR, total pulmonary; PVR, pulmonary vascular; LV, left ventricle.

the femoral arterial and pulmonary wedge pressures, but relatively small increment in the pulmonary arterial and right ventricular pressures. With a carefully regulated infusion the elevated systemic arterial pressure could be satisfactorily maintained over a period of an hour or more. Following cessation of angiotensin infusion, both the femoral arterial and pulmonary arterial pressures returned to control values within 2 or 3 minutes.

Figures 3 and 4 show a positive correlation between the increment in the stroke work against pressure and that in the diastolic pressure of the respective ventricle. In half of the cases the pulmonary wedge pressure rose above 12 mm. Hg and in three cases to 20 mm. Hg or higher during infusion of angiotensin, yet there was still an increase in the stroke work against pressure in each case. The change in the right ventricular work against pressure in a smaller number of cases also showed the same trend, even when the right ventricular diastolic pressure rose to 10 mm. Hg or greater.

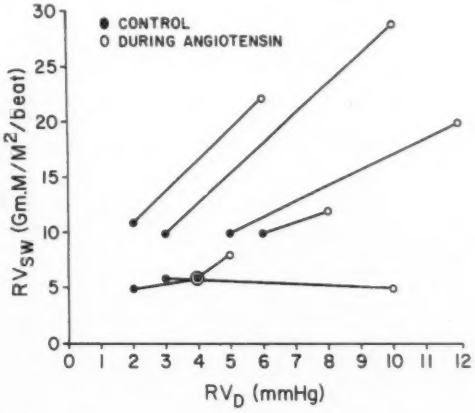

Figure 4

In six of seven patients during angiotensin infusion a positive correlation also was observed between the right ventricular work against pressure and the right ventricular end-diastolic pressure.

Animal Studies

The results are summarized in table 3. Continuous recording of the pressures showed that

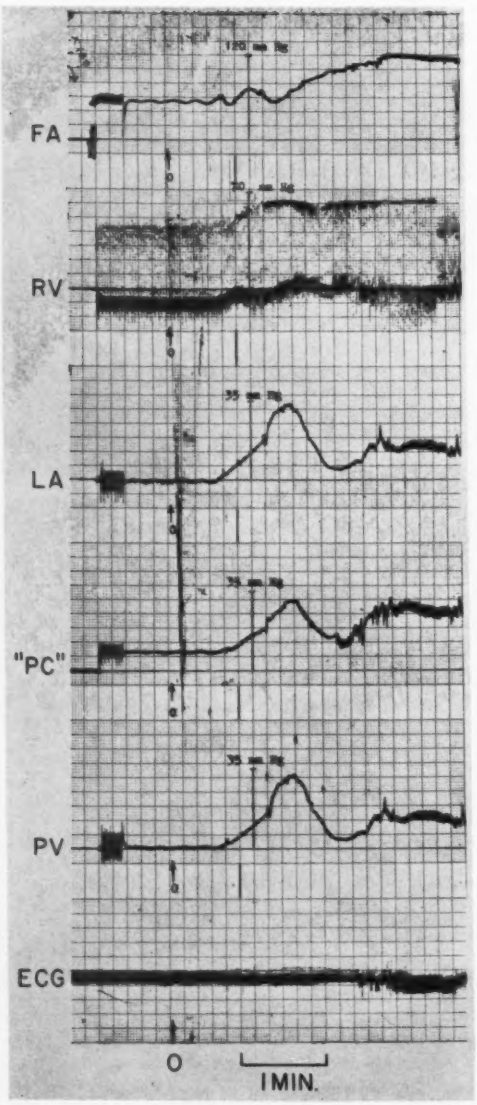

Figure 5

Simultaneous recordings of femoral arterial (FA), right ventricular (RV), left atrial (LA), pulmonary wedge ("PC"), and pulmonary venous (PV) pressures, and electrocardiogram (ECG) in a dog before and during angiotensin infusion. For about 20 seconds during the control periods the systolic and diastolic pressures were recorded. Subsequently, FA, LA, "PC", and PV mean pressures were obtained by electrical integration. Note a rise in all the pressures within 1 minute of the start of angiotensin infusion (1 μg./Kg./min.). During the second minute there was a maximal rise in LA, PV, and "PC" and RV diastolic pressures. Subsequently, the FA pressure rose steadily to a plateau while there was a sustained and moderate rise in both left and right ventricular diastolic pressures.

within 1 minute after the angiotensin infusion was started there was a uniform rise in pressures in the systemic circuit, pulmonary circuit, and all four cardiac chambers. In the next minute there was usually a rise in the left ventricular diastolic (represented by mean left atrial, pulmonary venous, and pulmonary wedge) and right ventricular diastolic pressures (fig. 5). The magnitude of the elevation in the left ventricular diastolic pressure was variable in different animals. Subsequently, the systemic arterial pressure rose steadily to a plateau, whereas a sustained and moderate rise in both left and right ventricular diastolic pressures was observed.

The increase in the systemic arterial pressure could be satisfactorily maintained as long as the constant infusion of angiotensin was continued. The optimal dose of angiotensin was found to be approximately 1 μg./Kg./min., which was 8 to 60 times the dose given to patients. Further increase of the dose (2 to 5 μg./Kg./min.) did not appreciably augment the systemic arterial pressure or left ventricular stroke work, although there was usually a further rise in left atrial and pulmonary arterial pressures.

Within 1 or 2 minutes following the cessation of angiotensin infusion all the pressures returned to control level, and in some instances the systemic arterial pressure was even lower than the control value. It was possible, however, to increase the systemic arterial pressure again if angiotensin infusion was resumed.

In two dogs severe systemic hypotension (i.e., femoral arterial systolic pressure less than 50 mm. Hg) produced by single or multiple intravenous injections of hexamethonium was satisfactorily counteracted by angiotensin infusion, although the magnitude of rise in systemic arterial pressure was not as high as

that observed with infusion of angiotensin alone (fig. 6).

As shown in table 3, rapid blood infusion caused an increase in cardiac output, stroke volume, left atrial and pulmonary arterial pressures, and left ventricular stroke work. The average pressure gradient from the pulmonary artery to the left atrium was widened. There was a slowing in heart rate but no appreciable change in the systemic arterial pressure. In contrast, angiotension infusion produced an increase in systemic arterial pressure and left ventricular stroke work, but no change in cardiac output, stroke volume, and heart rate. A slight increase in both left atrial and pulmonary arterial pressures was observed, but compared with the control value there was no appreciable change in the average pressure gradient from the pulmonary artery to the left atrium.

When both blood and angiotensin were infused simultaneously, the effects were additive, manifested particularly by the increase in left ventricular stroke work and left atrial and pulmonary arterial pressures. Representative left and right ventricular function curves during blood infusion with or without angiotensin are depicted in figure 7.

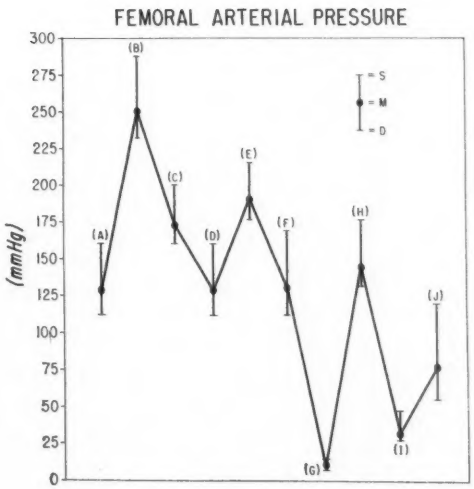

Figure 6

Femoral arterial pressure recorded in a dog during control periods (A, D, and F), with angiotensin infusion (B, E, H, and J), and following hexamethonium injections (G and I). The pressure at (C) was recorded during the time when angiotensin infusion was temporarily discontinued. Note the precipitous fall of the pressure after two hexamethonium injections (5 mg. on each occasion) which were followed by a moderate rise in pressure with angiotensin infusion.

Discussion

Angiotensin infused intravenously to both men and dogs is a very powerful pressor agent. It produces a prompt increase in total systemic resistance and systemic arterial pressure, most likely as a result of systemic arteriolar constriction.

During angiotensin infusion the consistent rise in the pulmonary wedge or left atrial pressure reflects a rise in the left ventricular diastolic or filling pressure. The increased left ventricular filling pressure accompanied by the alteration of systemic arterial pressure tracing, which was characterized by a prolonged upstroke time and the presence of an anacrotic notch, strongly suggests an increase in the "left ventricular" resistance. Such changes are frequently observed in patients with aortic stenosis.

It should be pointed out that in human studies, although there was a direct relationship between the increment in the respective ventricular stroke work and diastolic pressure, the data did not truly represent ventricular function curves either during the control period or during the period of angiotensin infusion. At best, they demonstrated that during angiotensin infusion there was an increase in the ventricular work at a higher level of filling pressure. We were able to obtain ventricular function curves in dogs, however, during both the control period and the period of angiotensin infusion by varying the left and right ventricular filling pressures. It was shown that the ventricular function curve during angiotensin infusion was shifted to the left and above that during the control period. In other words, more external work was performed at any given filling pressure during angiotensin infusion than during the control period. Thus angiotensin indeed caused an increase in the myocardial contractility as well as in the ven-

Table 3

*Hemodynamic Effects of Angiotensin or Rapid Blood Infusion, or Both, in Dogs**

Periods of study	No. of dogs	Cardiac output (L./min.)		Heart rate (beats/min.)		Stroke volume (ml./beat)		Mean pressures (mm. Hg)						Left ventricular stroke work (Gm.M./beat)	
								Femoral arterial		Pulmonary arterial		Left atrial			
		R	M	R	M	R	M	R	M	R	M	R	M	R	M
Control	5	1.18-1.94	1.50	140-190	158	8-10	9	56-120	93	5-6	6	0-4	3	6-16	12
Blood infusion	5	1.53-3.62	2.56	90-153	121	17-32	22	62-136	100	11-22	17	2-18	9	17-50	28
Control	5	0.50-1.98	1.35	100-160	138	3-17	10	28-112	76	4-6	5	0-4	2	1-19	12
Angiotensin	5	0.95-1.76	1.51	120-195	147	5-14	11	110-189	137	7-14	9	0-12	5	8-33	21
Angiotensin plus blood infusion	4	2.06-4.18	2.90	120-154	138	15-31	22	127-160	140	17-34	25	9-21	13	24-70	43

*The values of various parameters in a given dog were the average of two or more determinations obtained during a certain circulatory state.
R, range; M, mean.

tricular function.[19] It is reasonable to assume that similar results probably would have been obtained in man if ventricular function curves could be obtained during these two circulatory states. Nevertheless, the bulk of evidence would indicate that during angiotensin infusion, despite an increase in total systemic resistance and probably in "left ventricular" resistance, there was no compromise in ventricular function. In this regard, it is of special interest to comment on the pioneer studies of natural angiotensin in normal subjects made by Wilkins and Duncan in 1941.[8] They found that natural angiotensin produced arterial hypertension which was accompanied by an increase in venous pressure and, frequently, by a decrease in cardiac output and vital capacity and an increase in heart size and circulation time. They contributed these changes as probable signs of "myocardial failure." However, Bradley and Parker[9] studied the effects of similar preparation in man almost at the same time and did not find signs of "myocardial failure." Page and Bumpus[15] suspected that the presence of an impurity might have been responsible for part of Wilkins and Duncans' observation.

At that time there was no means to measure the pulmonary arterial and intracardiac pressures; therefore, it was not possible to correlate the increment in venous pressure with that in right ventricular stroke work. In the present study, a parallel increase in both right ventricular diastolic pressure and stroke work was observed in six of seven patients in whom the right ventricular and pulmonary arterial pressures were measured. One would anticipate similar findings in the study made by Wilkins and Duncan, should such measurements be available.

In animal experiments, when larger doses of angiotensin (more than 1 μg./Kg./min.) were given, there was a further rise in the left atrial pressure, with no appreciable change in the left ventricular stroke work. This may imply that in animals angiotensin given in smaller doses had its predominant action on myocardium, whereas with larger

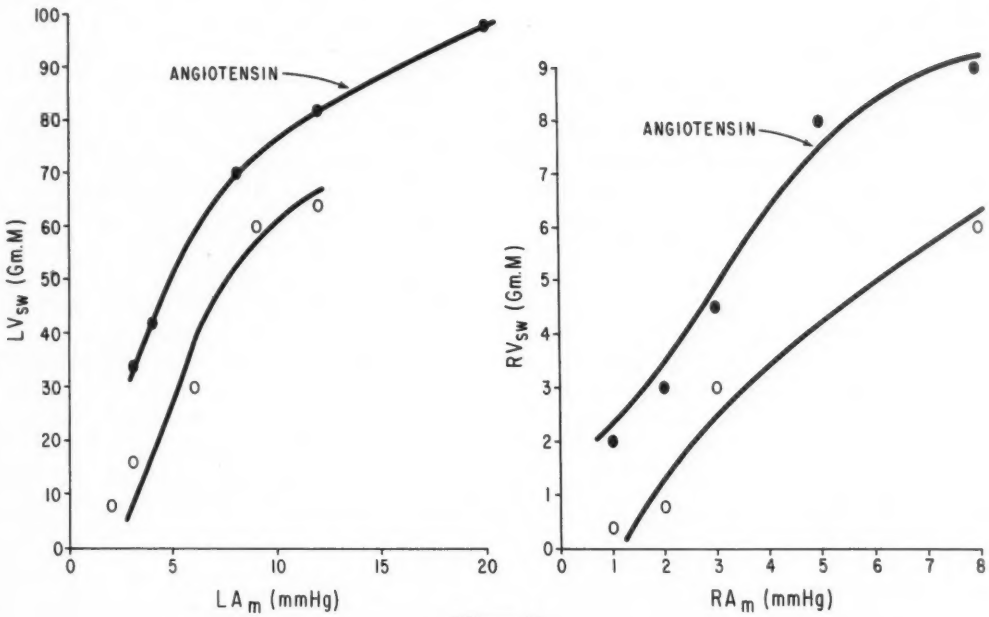

Figure 7

Left and right ventricular function curves during blood infusion with or without angiotensin after step-wise elevation of the reservoir. The respective ventricular stroke work was plotted against atrial mean pressure during each circulatory state. With angiotensin administration the ventricular function curves were shifted above and to the left of those without angiotensin. These changes indicated that more external work was performed at any given filling pressure with angiotensin infusion than without.

doses its action on the systemic arterioles became more manifest. These findings were quite similar to the results of the studies on Aramine reported by Sarnoff and co-workers.[20]

In most human subjects, and in all dogs, the increase in pulmonary arterial pressure appeared to be passive and secondary to the rise in left ventricular diastolic pressure, since there was little or inconsistent change in the pulmonary artery to left atrial (pulmonary wedge) pressure gradient. Similar observations were reported by Nelson and associates,[12] and by Sancetta,[14] when other preparations of angiotensin were used. The possibility of constriction of pulmonary veins probably can be ruled out, inasmuch as in dogs the changes in pulmonary wedge and left atrial pressures were identical.

Since the "central" blood volume in the patients of this series did not change significantly, the increase in pulmonary vascular pressures was probably not related to redistribution of blood volume from the peripheral to the pulmonary circulation.

Our unpublished observation[21] showed that in most patients with mitral valvular lesion angiotensin produced a consistent increase in both left atrial and pulmonary arterial pressures accompanied by a decrease in the true pulmonary blood volume. These findings strongly suggest that active vasoconstriction of the pulmonary vascular bed may occur in patients with mitral valvular disease. No comparable data were obtained in patients included in this series.

The prolongation of the total circulation time from femoral artery to femoral artery was more striking than that of the mean transit time from the pulmonary artery to the femoral artery. This difference strongly

suggests that slower circulation did occur in the systemic circuit probably as a result of acute systemic vasoconstriction and hypertension.

It would appear that in man the optimal dose of angiotensin infused intravenously is about 0.05 to 0.10 μg./Kg./min. Larger doses may cause severe headache and general discomfort, which were present in two of our patients. We have not observed some of the unpleasant manifestations, such as chilly sensation, piloerection, and difficulty in urination, frequently encountered during methoxamine (Vasoxyl) infusion. Furthermore, it also has the advantage over methoxamine in that the hypertensive effects can be repeatedly induced and terminated within a matter of several minutes.

As shown by other workers, angiotensin has been used effectively in the treatment of hypotension and shock in various disease states. It was found to be six to 10 times as potent as norepinephrine.[13] Furthermore, from our animal studies it is apparent that marked hypotension induced by the administration of a ganglion-blocking agent (i.e., hexamethonium) can be promptly counteracted by intravenous infusion of angiotensin. Therefore, there is a potential use of this vasopressor agent in the practice of anesthesiology, since in some instances it is urgent to raise promptly and effectively the systemic blood pressure that has been lowered by a ganglion-blocking agent for the purpose of a specific surgical procedure.

Summary and Conclusions

The effects of angiotensin (Hypertensin II CIBA) given by intravenous infusion on pulmonary circulation and ventricular function were studied in 16 normotensive patients and eight anesthetized dogs.

During angiotensin infusion the following changes were observed: (a) an increase in pressures in both systemic and pulmonary circuits and four cardiac chambers, and variable change in pulmonary artery-pulmonary wedge (or left atrial) pressure gradient; (b) slightly decreased or unchanged cardiac output and stroke volume; (c) significantly increased total systemic and total pulmonary resistances; (d) significant increase in stroke work of both ventricles; (e) significant prolongation in the circulation time from femoral artery to femoral artery and slight prolongation in mean transit time from pulmonary artery or right heart to the femoral artery and, (f) no significant alteration in total or "central" blood volume.

It is concluded that (a) angiotensin is a very powerful vasopressor agent and has its action primarily on the systemic circulation; (b) in the compensated human and canine hearts it also increases myocardial contractility and ventricular function; and (c) in patients without mitral valvular lesions or intracardiac shunts the hemodynamic changes in the pulmonary circulation are mostly secondary.

Acknowledgment

We wish to express our thanks and appreciation to Dr. Arthur Dutton, Assistant Professor of Radiation Biology and Scientist (Statistics), Atomic Energy Project, University of Rochester, for his help on the statistical aspect of this study. We are indebted to Drs. Gerald Glick, Frank W. Lovejoy, Jr., Michael R. McCredie, Celia Oakley, Clay Phillips, Jr., and Bernard F. Schreiner for their participation in the study.

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It is a sound rule rarely to diagnose conditions that occur rarely.—Sir Thomas Lewis. *Diseases of the Heart.* New York, The MacMillan Company, 1933, p. 127.

Radioisotope Scanning of the Precordial Distribution of Iodide in Patients with Myocardial Infarction

By DEAN T. MASON, M.D., ROBERT L. FRYE, M.D., AND HENRY N. WAGNER, JR., M.D.

RADIOISOTOPE scanning has proved useful as a means of diagnosing pericardial effusion.[1] Ten minutes after administration of human serum albumin labeled with radioiodine, the spatial distribution of the radioactivity throughout the central cardiovascular system is automatically measured and recorded photographically. The diagnosis of effusion is based on comparison of the scanning image of the cardiac blood pool with the roentgenographic image of the heart obtained while the patient is lying on the scanning table.

An additional use of scanning in the field of cardiovascular disease was suggested by Dreyfuss, Ben-Porath, and Menczel.[2] These authors had observed that I^{131}-labeled iodide concentrated in pulmonary infarcts, and postulated that necroses of the heart might also concentrate this isotope.

Patients with myocardial infarction were studied after the administration of I^{131}-labeled iodide. Iodide rather than iodinated albumin was used. Counting rates were recorded daily by means of a stationary scintillation detector over the chest wall. The counting rate over the electrocardiographic locations of leads V_3 and V_5 were determined over both left and right chest. In contrast to the results observed in control patients, all patients with myocardial infarction had at least a 20 per cent higher concentration of radioactivity on the left side of the chest than on the right. On the basis of this finding, the authors suggested that it might be possible to demonstrate areas of myocardial infarction by a radioisotope-scanning procedure, although they did not attempt this themselves.

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The present study was designed to evaluate the feasibility of outlining myocardial infarctions by a radioisotope scanning technic.

Methods

In essence, the technic consists of automatically recording the spatial distribution of a gamma-emitting radionuclide within the body and is more completely described elsewhere.[1] The scan is obtained with the patient lying in a supine position while two motors move a radiation detector back and forth automatically over the chest. The detector consists of a sodium iodide crystal, photomultiplier tube, and focusing collimator. The radiation coming from the iodine immediately beneath the probe is detected, amplified, and recorded automatically. Background radioactivity is minimized by means of a gamma-ray spectrometer. The radioactivity is utilized to activate a light that exposes x-ray film. The darkening of the film is a function of the amount of radioactivity beneath the detector. Immediately following the scanning procedure, a chest x-ray is taken with the patient lying on the scanning table. The scanning image is superimposed on the x-ray image of the heart by means of localizing markers on both scanning image and x-ray.

The scans were performed 24 hours after administration of 100 to 200 microcuries of NaI^{131}. This is another difference from the procedure used for detecting pericardial effusion in which case iodinated albumin rather than iodide is administered and the scanning procedure is performed shortly after the intravenous injection rather than 24 hours later. In the present study, all patients received potassium perchlorate prior to the administration of the radioiodine to decrease thyroid uptake of the isotope. Therefore, most of the administered radioiodine was excreted by the kidneys prior to the scanning procedure. Consequently, the radioactivity in the blood was low after 24 hours and any concentration of radioiodine in the area of myocardial infarction would appear as a localized darkened area on the scanning image. Immediately prior to the scanning procedure, we made precordial measurements of the radioiodine concentration beneath a stationary probe over the electrocardio-

Table 1

Description of Patients with Myocardial Infarctions

Patient (J.H.H. number)	Area of infarction (ECG)	Time after infarction scan performed (Days)	Dose radioiodine (μc.)	L:R radioactivity ratio	Localized concentration of radioiodine (plus or minus)
963184	Anterior	15	100, oral	1.5:1	+
944739	Diaphragmatic	16	100, oral	1.8:1	+
971408	Diaphragmatic	17	100, oral	1.9:1	−
113200	Anterior	16	100, oral	1.1:1	−
974711	Diaphragmatic	10	200, oral	1.05:1	−
490657	Diaphragmatic	16	200, oral	1.1:1	+
343602	Anterior	17	200, oral	1.4:1	−
177714	Diaphragmatic	12	200, oral	1.3:1	−
417326	Diaphragmatic	16	200, oral	1.1:1	−
867798	Anterior lateral diaphragmatic	8	200, oral	0.93:1	+
867798	Anterior lateral diaphragmatic	15	200, oral*	0.72:1	−
867798	Anterior lateral diaphragmatic	17	200, I.V.	1.1:1	+
799291	Not localized	10	200, I.V.	1.05:1	+
836501	Anterior	21	200, I.V.	1.2:1	+

*Radioiodine given 8 days prior to scan.

graphic positions left V_3 and right V_3. This part of the study duplicated the work of Dreyfuss et al. except that we utilized a 12-hole focusing collimator with a smaller field and better resolution.

A total of 14 scans in 12 patients with clinical and electrocardiographic evidence of myocardial infarction was obtained. In four control patients, the radioiodine content of whole blood and gastric juice was measured in a well-scintillation detector after 100 microcuries of intravenous radioiodine were administered.

Results

Figure 1 presents the results of the radioisotope scan in two patients with myocardial infarction, illustrating a localized concentration of radioiodine along the diaphragmatic border of the heart. This occurred in four of the 11 scans performed after oral administration of the radioiodine and in all three scans obtained after intravenous administration of the radioiodine. Six of 12 patients had a ratio of 1.2:1.0 or greater when precordial isotope measurements over the left chest were compared with a corresponding position over the right chest. Table 1 summarizes the results.

Although the radioiodine appeared concentrated along the diaphragmatic border of the heart, the possibility was considered that the collection of radioactive material might be in the stomach. Evidence obtained by comparing the concentration of radioactivity in a sample of gastric contents to that of simultaneous blood samples after intravenous radioiodine was administered supported the concept that the radioiodine was concentrated in the stomach. These data are presented in table 2.

Discussion

The present results strongly suggest that the concentration of radioiodine that occurs over the left chest 24 hours after the administration of I^{131}-labeled iodide is due to radioiodine concentrated in the cardia of the stomach. This was observed after the intravenous as well as the oral administration of the iodide. Since saliva contains a high concentration of radioiodine, it is possible that swallowed saliva plays some role in the collection of radioiodine in the stomach. It has been reported, however, that the stomach itself has a remarkable capacity to concentrate iodide.[3-5]

Since gastric emptying is delayed in patients who lie quietly in bed, one can postulate

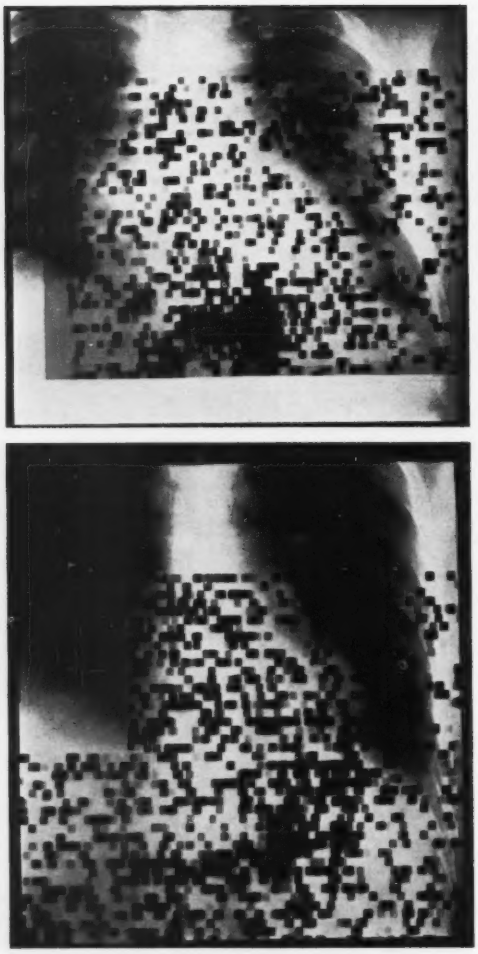

Figure 1

Top. *Scintiscan of patient (963184) with myocardial infarction.* Bottom. *Scintiscan of patient (944739) with myocardial infarction.*

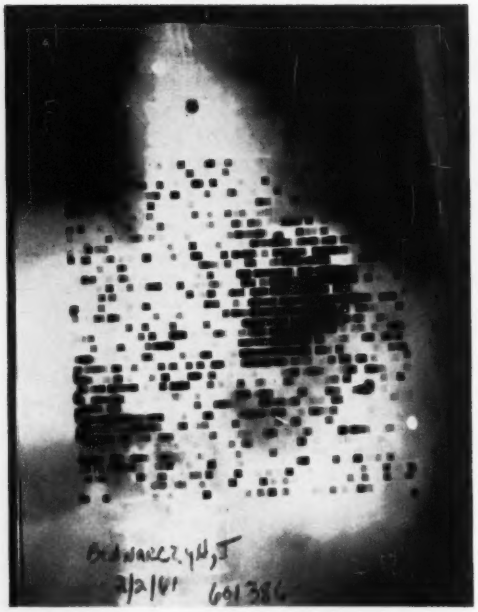

Figure 2

Scintiscan of control patient (601380).

Table 2

Gastric and Blood Activity after Intravenous Radioiodine Administration

Patient (J.H.H. number)	Time after radioiodine administered (hours)	Radioiodine activity ratio (gastric/blood)
(1) 977260	24	3:1
(2) 466899	42	5:1
(3) 979280	24	1:1
	49	1:1
(4) 601386	6	8:1
	28	8:1
	100	20:1
	120	13:1

that the enforced bed rest in patients with myocardial infarction would lead to a higher mean concentration of secreted radioiodine in the cardia than that found in patients in whom bed rest is not so strictly enforced. The distribution of radioiodine in the stomach of a normal person kept at rest for 24 hours after the administration of 100 microcuries of sodium iodide (I^{131}) *intravenously* is shown in figure 2. The localization of this material in the stomach can be seen superimposed over barium contained in the cardia of the stomach.

Despite the failure of the present investigation to demonstrate the feasibility of outlining areas of myocardial infarction by means of radioiodine, future attempts to scan areas of myocardial infarction with other isotopes may be successful. The present data, however, emphasize the need for caution in interpretation of precordial scans obtained with radioiodine.

Summary

Precordial scanning of the distribution of radioiodine (I^{131}-labeled iodide) in patients with myocardial infarction has been suggested by others as a means of delineating the infarcted area.

Attempts to localize radioiodine in 14 precordial scans of 12 patients with myocardial infarction resulted in the demonstration of localized areas of radioactivity in seven scans. This collection of radioactivity was found to be within the stomach, resulting from the normal concentration of radioiodine that occurs in gastric secretions.

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Thomas Sydenham
1624–1689

Thus it was that Sydenham came to seem to his contemporaries "the English Hippocrates." Unquestionably his medical art and science had in many respects the characteristics of a reaction, and Sydenham regarded himself as a Hippocratist. Like Hippocrates, the basic principle of his medical thinking was the humoral pathology, and like Hippocrates his general outlook upon illness was that it was a natural healing process. Nevertheless there lay a whole world between the two. The decisive difference between them becomes plain in respect of their divergent outlook upon illness as soon as they quit the domain of the general. Hippocrates recognized only disease, not diseases. He knew only sick individuals, only cases of illness. The patient and his malady were for him inseparably connected as a unique happening, one which would never recur. But what Sydenham saw above all in the patient, what he wrenched forth to contemplate, was the typical, the pathological process which he had observed in others before and expected to see in others again. In every patient there appeared a specific kind of illness. For him maladies were entities, and his outlook upon illness was, therefore, ontological. Hippocrates wrote the histories of sick persons, but Sydenham wrote the history of diseases.—Henry E. Sigerist, M.D. *The Great Doctors.* New York, W. W. Norton & Co., Inc., 1933, p. 181.

Corrective Surgery for Tetralogy of Fallot

Evaluation of Results

By EARLE B. KAY, M.D., CID NOGUEIRA, M.D., DAVID MENDELSOHN, JR., M.D., AND HENRY A. ZIMMERMAN, M.D.

A SUFFICIENT NUMBER of patients with tetralogy of Fallot have now had definitive correction by open-heart surgery, made possible by the use of the pump-oxygenator and extracorporeal circulation, to make a comparative analysis of the results attained between open definitive correction of the defects and the results of the earlier bypass shunt procedures of the Blalock-Taussig[1] or Potts[2], and the pulmonary valvulotomy or infundibulectomy technic initiated by Brock,[3] and perhaps to delineate the current role of these available procedures to the present care of patients with this condition.

The increased pulmonary blood flow afforded by systemic-pulmonary artery anastomosis and infundibulectomy was a dramatic development in the palliation of these otherwise hopeless children. Follow-up studies[4-6] of the patients so treated have demonstrated in ensuing years an increasing diminution of what appeared to be good palliation during the first several years following surgery from late complications such as bacterial endocarditis, cerebral abscesses, heart failure, and thrombosis of the anastomosis. Later morbidity or death has been due to the patient outgrowing the anastomosis with recurrence of the original disability; or in some instances due to the development of pulmonary hypertension caused by further increase in the size of the anastomosis with growth.

Pulmonary valvulotomy or infundibular resection represented a further step forward in a more objective treatment of tetralogy of Fallot. According to Campbell and Deucher[7] however, the late results of the direct and indirect methods were very similar. Loss of improvement following valvulotomy or infundibular resection was due either to recurrence of the obstruction in the right ventricular outflow tract or to the development of a large left-to-right shunt created by the operation because of the inability with this technic to correct associated ventricular septal defect.

The development of safe extracorporeal technics, the advances in intracardiac corrective surgery, and the use of cardioplegia have made possible the complete repair of tetralogy of Fallot.[8, 9] In view of the conflicting results reported with the palliative procedures, and the scarcity of reports in the literature of postoperative hemodynamic evaluation in patients submitted to a corrective operation by the open technic, this report appears to be pertinent.

The criteria for postoperative evaluation of benefit gained in the past have for the most part been the clinical condition of the patient, the status of cyanosis, the degree of polycythemia, and the hemoglobin level. The evaluation of the late results attained by the open corrective method for tetralogy of Fallot should also include hemodynamic improvement as demonstrated by cardiac catheterization studies in addition to the clinical evaluation.

Series

This report concerns the repair of tetralogy of Fallot in a series of 50 consecutive patients. The method of correction is described and the results are analyzed. Complete evaluation including cardiac catheterization studies of a group of patients operated upon 1 to 5 years previously is presented.

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In all patients the diagnosis of tetralogy of Fallot was clinically established and complemented by laboratory studies. All patients were cyanotic. Polycythemia and high hemoglobin levels were always present. Clubbing was present in all patients but the two very young ones. The age varied from 12 months to 42 years, and the majority of the patients were in the younger age group. Four patients had had previous Blalock operations. In three of them the anastomosis was patent. One patient had had a Brock procedure with a good initial result but with gradual recurrence of symptoms 3 years after surgery.

Preoperative Evaluation

Although the diagnosis of tetralogy of Fallot can be established clinically in the majority of instances, a more objective preoperative evaluation is indispensable in order to gain more information about the hemodynamic alterations and to provide details about the anatomic variations of the defects. Electrocardiographic and roentgenologic examinations, as well as catheterization studies were performed in each patient in this series. For the past several years cineangiocardiographic studies have been done routinely. This is the most objective method of obtaining reliable information preoperatively concerning the anatomic condition of the pulmonary outflow tract. The visualization of the ventricular septum and the ventricular septal defect aided in establishing the differential diagnosis between tetralogy of Fallot and patients with a single ventricle and pulmonary stenosis. It further provided information relative to atresia of the pulmonary outflow tract and pulmonary artery. It aided in evaluating the efficacy of corrective surgery when associated with marked pulmonary atresia in instances of pseudotruncus arteriosus.

Contrary to the policy of others, small infants (less than 20 lb. of body weight) have been followed by a careful medical supportive management. The risk of any kind of surgery in these patients has been great and does not, in our minds, justify surgical intervention before these children grow larger. These cyanotic infants in the past have been frequently hospitalized for acute supportive therapy during the first year of life. During the past 5 years only one infant died during this first year of life under this policy. All others survived until the time they became better risks for surgical treatment. The performance of shunt operations in this group of small infants has not been satisfactory due to the high operative mortality and incidence of thrombosis of the anastomosis.

Operative Approach

A bilateral thoracotomy was used initially. During the last 2 years a longitudinal sternotomy has been employed. Postoperatively, pain and pulmonary complications were less with the sternal-splitting incision. The pleural spaces were kept closed until the end of surgery, avoiding manipulation and trauma of the lungs. At the end of surgery the right pleural space was opened to provide thoracotomy drainage of the mediastinal structures.

Extracorporeal circulation for all patients was provided with a Kay-Cross pump oxygenator. One of the superficial femoral arteries was cannulated for perfusion. The management of these patients and the physiologic controls of the perfusion have been previously reported.[10] Heparin (1 mg./lb.) was given prior to cannulation. With the patient on total heart-lung bypass, elective cardiac arrest was induced, the cardiotomy was performed, and the defects were repaired under direct vision. In the three patients in whom a previous Blalock anastomosis was still patent, the shunt was interrupted at the moment the bypass was started.

Elective cardiac arrest was employed to obtain a bloodless, motionless field, which afforded perfect identification and repair of the ventricular septal defect. In 42 patients potassium chloride was the cardioplegic drug. In all instances cardiac rhythmicity was restored without difficulty. In the past year, however, hypothermic cardiac arrest has been used because it afforded greater myocardial protection without the supposed deleterious effects of potassium arrest.[11] Frequently, pericardial irrigation with the same solution was used to supplement this method for continued

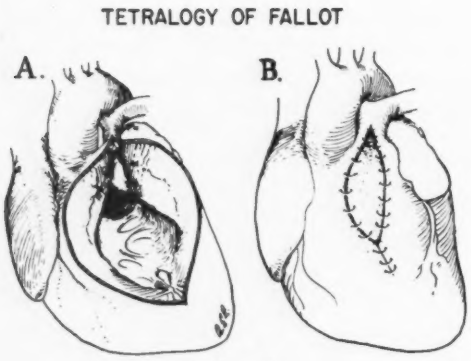

Figure 1

Diagrammatic illustration of technic employed in increasing the size of the right ventricular outflow tract.

hypothermia. Intracardiac repair of tetralogy of Fallot is a time-consuming procedure (45 to 60 minutes) and extra protection to the myocardium was gained by this means of applying hypothermia.

The cardiotomy was made in the outflow tract of the right ventricle and carefully extended to permit good exposure of the intracardiac structures. Anomalous branches of the coronary arteries may cross this area that should not be sacrificed without proper evaluation. The infundibulum and excess muscle mass obstructing the ventricular outflow tract was resected under direct vision and a pulmonary valvulotomy was performed when necessary.

The ventricular septal defect was accurately identified and a small sump was introduced into the left ventricle, via the septal defect, in order to maintain a bloodless field. This same sump was used for decompression of the left ventricle during the recovery phase of the elective cardiac arrest.

Individual 4-0 silk sutures were placed at the edges of the septal defect and used for suturing an Ivalon* patch. Special care was exercised in order to avoid inclusion of elements of the conductive system. The careful placement of interrupted sutures and the use of a patch in the repair of the defect were essential factors in the prevention of operative heart block. Atrioventricular block associated with closure of the septal defect has never occurred. Disturbances in the right ventricular conduction system have been frequent after repair of tetralogy of Fallot, and have been attributed to extensive resection of the infundibulum.[12] In tetralogy of Fallot, the ventricular septal defect was generally due to a complete absence of the membranous septum. In our experience, simple suture closure used in a few instances has not been as satisfactory a method of closure.[13] The use of an Ivalon patch insured a permanent closure of the septal defect without tension, and the interrupted sutures used for its fixation avoided damage to the conduction system. Before the ventricular septal defect was completely closed, the aortic clamp was released and the coronary flow was re-established. If ventricular fibrillation occurred and did not revert spontaneously, electric defibrillation (60 to 100 volts at 0.1 second) was used.

During elective hypothermic cardiac arrest, the temperature of the myocardium was monitored by a Yellow Springs needle thermistor. Electric defibrillation was attempted only after the myocardial temperature reached 32 C. When a good heart beat was re-established, the sump was removed from the left ventricle and the remaining sutures were tied.

In spite of extensive infundibular resection, the majority of the patients (70 per cent) had an elliptical patch of heavily compressed Ivalon (10 to 1 mm.) sutured to the edges of the cardiotomy in the ventricular outflow tract to increase further the size of this chamber and to avoid residual obstruction (fig. 1). Upon occasions it has been necessary to extend this plastic graft for varying distances across the pulmonary valve and into the pulmonary conus in order to obtain a satisfactory right ventricular pulmonary artery pathway. The correction of the pulmonary stenosis was a vital phase of the repair of tetralogy of Fallot. Complete closure of the septal defect, without assuring an adequate ventricular pulmonary artery outflow tract, precipitates right ventricular failure in the immediate

*Commercial brand of polyvinol sponge.

Table 1

Hemodynamic Studies before and after Surgery Demonstrating the Benefit Obtained by Open Correction of Tetralogy of Fallot

Name	Age	Pressure, right ventricle		Pressure, pulmonary artery		Arterial saturation (%)		Residual defect	Comment
		Pre.	Post.	Pre.	Post.	Pre.	Post.	Post-Op.	
R.F.	20	128/16	75/—3	—	40/12	69.4	96.5	Small L-to-R shunt	Previous Blalock (thrombosed)
G.S.	6	110/—10	27/1	—	26/8	48.5	96.7	No shunt	
K.H	6	77/8	45/0	23/10	36/9	75.6	94.9	No shunt	Previous Brock
J.E.	6	135/—10	38/0	15/3	32/10	32.4	93.4	No shunt	
L.McK.	3	102/—7	35/—2	—	17/7	79.2	93.3	No shunt	
R.R.	19	120/—2	65/0	—	50/12	72.3	92.4	L-to-R shunt	
D.L.	6	126/—3	28/0	8/3	26/9	76.5	94	No shunt	
K.H.	12	85/11	40/—2	15/4	20/6	81.6	96.7	No shunt	Previous Blalock (open)
J.M.	14	112/—5	35/0	—	25/9	77	96	No shunt	Previous Blalock (open)
B.R.	7	110/—1	30/0	—	27/8	81	95	No shunt	Previous Blalock (open)
H.C.	6	110/—5	40/0	—	26/9	52.3	93.4	No shunt	
N.E.	12	105/0	31/0	15/6	24/9	84	97.4	No shunt	
M.F.	4	125/0	22/0	—	21/8	59.3	98	No shunt	
K.T.	6	112/0	28/0	32/10	26/7	81	96	No shunt	
R.P.	8	110/—2	32/0	—	30/10	80.7	95	No shunt	

postoperative period. This was the main cause of failure initially when grafting of the outflow tract was not used.

After the definitive surgery was accomplished and the heart was able to take over the circulation, protamine was given (1 mg./lb.) and the cannulae were removed. Careful hemostasis was necessary. It is our impression that cyanotic patients have a higher bleeding tendency than acyanotic ones. Often it was necessary to give these patients larger doses of protamine and vitamin K_1 to re-establish the clotting mechanism.

Pressures were routinely taken in the right ventricle and pulmonary artery before and after the bypass in order to evaluate the repair of the pulmonary stenosis. Postoperatively special care was taken to maintain a normal blood volume by replacing thoracotomy drainage with fresh whole blood. In addition, five per cent glucose was given during the first 48 hours (500 ml./M.^{2} of body surface). The patients were placed in an Eliot hood, where a high concentration of oxygen (75 to 85 per cent) was maintained during the first 24 hours. The airway was kept clean, and tracheal aspiration was performed with a laryngoscope as indicated. Tracheotomy was employed only once early in this series.

Results of Corrective Surgery

The over-all 5-year mortality was 18 per cent. During the last 2 years, 20 patients have had complete correction of tetralogy of Fallot with an operative mortality of 15 per cent. The higher mortality rate observed during the first 2½ years was inherent in the developmental phases of extracorporeal circulation and surgical technics for repair of this complex malformation. Forty-one of the fifty patients are alive and well. Of the nine operative deaths, those occurring early in the series were for the most part due to poor correction of the infundibular stenosis in the presence of a complete closure of the septal defect. Attempts to correct hearts with too atretic pul-

monary arteries were the next frequent cause of failure. Three patients, also among the first 25 cases operated upon, died in consequence of anuria secondary to high hemolysis during perfusion. With added experience and improvement in perfusion technics anuria is no longer a complication. A 12-month-old baby succumbed on the third postoperative day as a result of a subdural hematoma. Only one patient died in the late postoperative period. This was a 20-year-old patient who died 2½ years postoperatively after a short hospitalization for bacterial endocarditis. During the previous 2½ years he was able to attend school and carry on normal physical activities. Postmortem examination revealed that the ventricular septal defect was not completely closed and there was evidence of subacute bacterial endocarditis involving the tricuspid valve. The Ivalon grafts in the right ventricular outflow tract and ventricular septum were well incorporated, pliable, and covered by endothelium. There was no evidence of calcification or aneurysmal dilatation of the grafts.

The remaining 41 patients with tetralogy of Fallot operated upon during this 5-year period are alive, asymptomatic, and have normal physical activity. The cyanosis and polycythemia have disappeared and the hemoglobin levels are normal. Postoperative roentgenologic studies revealed normal-sized hearts and normal pulmonary vasculature. Complete postoperative evaluation including hemodynamic studies have now been performed in 15 of these patients from 1½ to 3 years postoperatively. The pertinent data are reported in table 1.

An analysis of these 15 patients demonstrates that in 13 of them a complete hemodynamic correction was accomplished. In two patients, a small left-to-right shunt still existed. One of these patients (R. R.) although clinically well for 2½ years, developed subacute bacterial endocarditis and died as noted above. This was the only late death in the series. The other patient (R.F.) with a residual left-to-right shunt also has a gradient between right ventricle and pulmonary artery (33 mm. Hg). He has had excellent clinical improvement, is asymptomatic, and pursues normal activity, over 3 years following surgery. The arterial saturation has increased from 69.4 to 96.5 per cent.

Conclusion

Definitive surgical correction of tetralogy of Fallot by the open technic has not been accompanied by a higher operative mortality than that associated with the shunt operations. As a result of the surgical technics being directed at the correction of the defects, greater improvement approximating normal is attained.

Summary

Fifty patients with tetralogy of Fallot have had surgical correction of their complex defects made possible by the open technic during the past 5 years. The overall 5-year operative mortality was 18 per cent. This was reduced to 15 per cent during the past 2 years in 20 patients. Forty-one of the patients are alive, asymptomatic, and have normal physical activity. Ffteen patients have had cardiac evaluation studies including cardiac catheterization from 1½ to 3 years postoperatively. Thirteen patients had normal cardiac hemodynamics. In only two patients was there evidence of incomplete hemodynamic improvement even though marked clinical improvement was gained.

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On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves

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The morbid affections of the valves and aorta permitting this regurgitation are the following.

1st, The valves may be absorbed in patches, and thus become reticulated and present holes, through which the blood flows back into the ventricle . . .

2nd, One or more of the valves may be ruptured; the ruptured valves, when pressed, flapping back into the ventricle instead of catching and supporting the column of blood in the aorta, the blood then regurgitating through the space left by the broken valves . . .

3rd, The valves may be tightened or curled in against the sides of the aorta, so that they cannot spread across its mouth; and an opening is then left between the valves, in the centre of the vessel, through which the blood flows freely back into the ventricle . . .

4th, The valves without any proper organic lesion may be rendered inadequate to their function by dilatation of the mouth of the aorta. The aorta, affected by aneurism, or dilated, as it frequently is in elderly persons, about its arch, will sometimes have the dilatation extending to the mouth of the vessel, and in such a case, the valves become inadequate to their function, not from any disease in themselves, but from the mouth of the aorta dilating to such a diameter, as to render the valves unable to meet in its centre; the blood then, as in the other instances, regurgitates freely into the ventricle.

Myocardial Metabolism in Progressive Muscular Dystrophy

By J. F. SUNDERMEYER, M.D., S. GUDBJARNASON, PH.D., V. E. WENDT, M.D., P. B. DEN BAKKER, M.D., AND R. J. BING, M.D.

MYOCARDIAL as well as skeletal muscle involvement occurs in a high proportion of cases of human progressive muscular dystrophy. This cardiac involvement constitutes a specific cardiomyopathy. Clinical evidence of myocardial involvement by the dystrophic process includes labile tachycardia in over 50 per cent of cases, congestive heart failure, various arrhythmias, cardiac murmurs, and cardiomegaly.[1-5] Electrocardiographic abnormalities occur in up to 80 per cent of patients.[3] These changes include sinus tachycardia, bundle-branch block, premature ventricular contractions, shortened P-R intervals, T-wave changes, elevation of S-T segments, and abnormal Q waves.[1,2,3,6-8] Pathologically, the myocardium shows the characteristic gross and histopathologic changes of skeletal muscle as seen in progressive muscular dystrophy, except that the myocardium is usually not so severely involved.[3,7] In addition, specific cardiac lesions include increased subepicardial fat and occasional epicardial thickening.[7] Subendocardial fibroelastosis may also occur.[1,9]

The clinical findings and the pathologic changes of the heart in progressive muscular dystrophy have recently been reviewed by Levin, Baens and Weinberg.[1]

Although the metabolic changes of skeletal muscle in human progressive muscular dystrophy have been studied extensively, the metabolism of the myocardium has not been investigated. It is the purpose of this communication to report the cardiac metabolism of 11 patients suffering from this disease.

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Materials and Methods

A total of 11 patients with progressive muscular dystrophy was studied by means of coronary sinus catheterization.[10] The patients ranged in age from 9 to 41 years; however, most of them were 16 to 22 years old. The average duration of the disease in this group was 12 years (table 1). The shortest duration was 4 years and the longest 19. Nine of the 11 patients had the pseudohypertrophic type of muscular dystrophy, and two (F.D. and J.G.) had the facioscapulohumeral type (table 1). The electrocardiographic changes are recorded in table 2. All these patients were physically seriously handicapped. All but two (F.D. and J.G., table 1) were confined to a wheelchair, and A.L. (table 1) had marked difficulties in walking. The patients were postabsorptive, and none was premedicated. Two patients (J.G. and M.Z.) were studied at rest and during exercise. Exercise consisted of moving the legs against a resistance. The work they performed was estimated to be about 20 Kg. meters per minute.

Coronary blood flow was measured by the nitrous oxide desaturation method in four patients as previously described.[11] Cardiac output was measured in six of the 11 patients by the Stewart-Hamilton method by injecting cardiogreen dye into the right atrium and sampling through a Gilford densitometer from either the brachial or the femoral artery.[12,13]

Simultaneous coronary sinus and either brachial or femoral arterial blood samples were drawn for the determination of oxygen, glucose, inorganic phosphate, pyruvate, lactate, and for malic dehydrogenase and aldolase activities. Blood oxygen concentration was determined by the manometric method of Van Slyke and Neill.[14] Glucose was determined by the method of Hugget and Nixon[15] and pyruvate was also measured enzymatically.[16] Lactate was determined by a method modified from Hohorst,[17] inorganic phosphate by the method of Wahler and Wollenberger[18]; malic dehydrogenase activity in plasma was measured as previously reported,[19] and plasma aldolase activity by means of a combined enzymatic test.[20]

Hereafter, differences in concentrations of substrates or the activity of enzymes between the

Table 1

Clinical Data on Eleven Patients with Progressive Muscular Dystrophy

Name of patient, age, and type of PMD	Sex	Date studied	Age of patient at onset of PMD	Electro-cardio-gram	Clinical laboratory			
					Urine creatine mg./24 hr.	Urine creatinine Gm./24 hr.	S-GOT units	S-LD units
R. J. 22 D	M	11/15/60	5	A	1810	0.7	57	390
G. P. 17 D	M	11/21/60	Infancy	A	297	0.2	15	130
F. D. 41 FSH	F	12/20/60	22	A	622	0.75	18	150
R. Mc. 10 D	M	1/6/61	2	N	292	0.2	88	1480
A. L. 9 D	M	2/7/61	5	A	392	0.3	102	1100
J. G. 18 FSH	M	2/28/61	Infancy	N	818	0.9	40	660
S. S. 20 D	M	3/7/61	13	A	1095	0.3	34	280
L. F. 16 D	M	3/9/61	3	A	253	0.2	37	150
B. M. 17 D	M	3/28/61	5	N	368	0.2	63	550
M. Z. 22 D	M	5/9/61	5	A	1179	0.9	95	470
L. D. 10 D	M	5/24/61	5	A	1306	0.3	89	1040

Abbreviations: PMD, progressive muscular dystrophy; S-GOT, serum glutamic-oxalacetic transaminase; S-LD, serum lactic dehydrogenase; D, Duchenne; FSH, facioscapulohumeral; A, abnormal; N, normal.

arterial and coronary sinus blood will be referred to as myocardial balances. A positive myocardial balance indicates a lower value in the coronary sinus blood than in the arterial blood; when the balance is negative, the value in the coronary sinus blood exceeds that in arterial blood.

Calculations

The per cent glucose oxygen extraction ratio was determined from the coronary arteriovenous differences of glucose and oxygen as described before:[21]

Glucose oxygen extraction ratio per cent = $\frac{O_2 \text{ equivalent of extracted glucose}}{\text{myocardial oxygen extraction}} \times 100$. The oxygen equivalent of glucose is 0.75 × mg. per cent of glucose extraction.

The ratio of the molar concentration of lactate to pyruvate is a reflection of the ratio of the molar concentration of DPNH to DPN.[22] The ratio of DPNH to DPN determines the oxidation-reduction potential of the system. Therefore, it is possible to determine the oxidation-reduction potential (E_h or redox potential) of the arterial and venous blood from the ratio of the molar concentration of lactate to that of pyruvate $\frac{(La)}{(Py)}$. Klingenberg and Bucher[22] state that the oxidation-reduction potential of the lactate-pyruvate system in blood and in the normal resting tissues are very close to each other. However, they arrived at this conclusion primarily through their work on the liver.[23] Nevertheless, it has been shown in this laboratory that changes in the oxidation-reduction

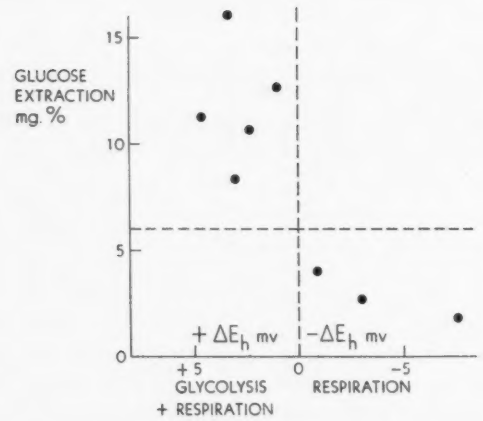

Figure 1

The differences in oxidation-reduction potentials between arterial and coronary venous blood are plotted against the myocardial glucose extraction. Negative coronary arteriovenous differences in oxidation-reduction potentials are associated with low glucose extractions; positive coronary arteriovenous differences in oxidation-reduction potential are associated with a higher myocardial glucose extraction. (Δ $E_h$mv represents the coronary arteriovenous difference in oxidation-reduction potential expressed as millivolts. A positive difference in oxidation-reduction potential suggests anaerobic metabolism.)

potential of the myocardium were reflected by those occurring in coronary sinus blood as calculated from the ratio $\frac{La}{Py}$.[24] The redox potential of the extramitochondrial DPN-DPNH system (E_h) has been estimated at −240 mv.[25] The redox potential is calculated from the formula

$$E_h = E_o + \frac{RT}{nF} \ln \frac{(OX)}{(RED)}$$

Where E_o is the redox potential when the oxidized substrate (OX) equals the reduced (RED). The value for the pyruvate-lactate system is −204 mv.[26] and the value for

$$\frac{RT}{nF} \ln \frac{(OX)}{(RED)} = 30.7 \log \frac{(OX)}{(RED)}$$

(R is the gas constant, T the absolute temperature, n represents the number of electrons, and F the faraday).[27] Thus, by substitution:

$$E_h = -204 + 30.7 \log \frac{(Py)}{(La)}$$

The change in redox potential across the heart is determined by substracting the venous from the arterial redox potentials. A positive difference in oxidation-reduction potential between the arterial and coronary sinus blood indicates a relative increase in the ratio $\frac{La}{Py}$ in the coronary venous blood and therefore a shift toward anaerobic metabolism by the myocardial cells.

Table 2

Electrocardiographic Changes in Eight Patients with Progressive Muscular Dystrophy

Name	Electrocardiographic abnormalities
R. J.	Deep Q in lead III Abnormal Q in leads V_5, V_7 S-T segment straightened in leads I, V_5, V_6, V_7 T wave small, diphasic in leads I, V_5, V_6, V_7
G. P.	Had right bundle-branch block on 10/10/60 Normal tracing on 11/22/60
F. D.	6/21/60 T waves very small in standard and unipolar limb leads V_5, V_6, V_7, diphasic in leads II, III, aV_R, aV_F. S-T segment straightened in all leads except V_1, V_2, V_3. 12/19/60 Improved but nonspecific damage still present
A. L.	Sinus tachycardia T small, diphasic in lead III
S. S.	Abnormal QI on 3/8/61 Abnormal QI plus elevated S-T segments in leads V_1 through V_7 on 7/6/60
L. F.	3/8/61 T inverted in lead III and diphasic in aV_F. Deep Q < .03 second in leads V_5, V_7. 9/20/60 Sinus tachycardia
M. Z.	Ventricular premature contraction S-T straightened and T wave flat in lead III
L. D.	P-R 0.08 second Deep but not prolonged Qs in leads V_5, V_6, V_7

Results

Cardiac indices ranged from 3.7 to 5.6, and the average for the group was 4.7 L. per minute per square meter of body surface (table 3). Thus, all the individuals had elevated cardiac outputs. The coronary blood flows in the four patients in whom it was determined were in the range of 53 to 92, with an average of 72 ml. per minute per 100 Gm. of left ventricle. This is within the normal range (table 3).

The biochemical data are arranged in table 3. The pyruvate and lactate balances were positive in all patients except two (L.F. and J. G.). Glucose was extracted by all patients; its extraction appeared to be a function of the arterial glucose concentration, as has been

previously reported.[21] The inorganic phosphate concentration in blood was elevated, confirming the findings of Danowski and coworkers.[28] There was no significant myocardial extraction or release of inorganic phosphate. The malic dehydrogenase activity in plasma was above normal in four of the eight patients; the myocardial balance of this enzyme was negative in two patients (B.M. and M.Z.), becoming positive in one (M.Z.) during exercise (table 3). The serum aldolase was elevated in four of the seven patients in whom it was determined. In one of these (J.G.) the positive myocardial balance became negative on exercise (table 3). The oxygen extraction by the heart ranged from 8.6 vol. per cent to 12.3 vol. per cent, with an average of 11.1 vol. per cent in 10 patients. These values are slightly elevated. The myocardial glucose oxygen extraction ratio was less than 100 per cent in all individuals, demonstrating breakdown of substrates other than glucose. The coronary arteriovenous redox potential differences were positive in most of the patients, indicating a shift toward glycolysis.

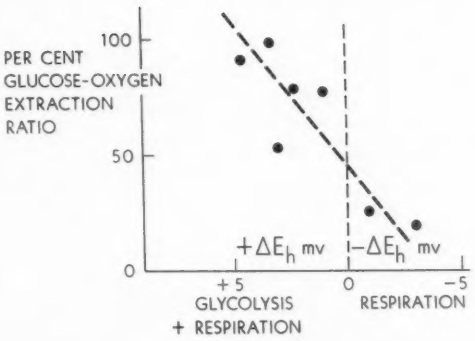

Figure 2

The per cent myocardial glucose oxygen extraction ratio is plotted against the coronary arteriovenous difference in oxidation-reduction potential. The myocardial glucose oxygen extraction ratio is less than 100 per cent in all patients with muscular dystrophy, suggesting usage of substrates other than glucose. As the per cent glucose oxygen extraction ratio rises, the coronary arteriovenous difference in oxidation-reduction potential becomes more positive.

Discussion

The relationship of the myocardial extraction of glucose to the difference in the redox potential existing between arterial and coronary vein blood is illustrated in figure 1. It may be seen that the more positive coronary arteriovenous redox potential differences are accompanied by a higher myocardial glucose extraction, the myocardial glucose extraction and the ratio $\frac{La}{Py}$ increasing together. This relationship indicates that the increased extraction of glucose is accompanied by a rise in glycolysis rather than respiration.

Figure 2 illustrates the relationship between the per cent glucose oxygen extraction ratio and the differences in coronary arteriovenous redox potentials. As already indicated in figure 1, most of the patients had positive coronary arteriovenous differences in redox potentials. As shown in figure 2, glucose oxygen extraction ratios are less than 100 per cent in all patients studied, indicating myocardial breakdown of substrates other than glucose. As the coronary arteriovenous redox potential differences become more positive, the per cent glucose oxygen extraction ratio increases (fig. 2). Apparently aerobic glycolysis occurs, since in the presence of sufficient oxygen to account for the oxidation of all the glucose extracted, an increase in the ratio $\frac{La}{Py}$ is present.

The blood concentration of inorganic phosphate is elevated in all seven patients in whom this determination was carried out. Figure 3 illustrates the relationship between the myocardial glucose extraction and the blood inorganic phosphate concentrations. As may be seen, there is a linear relationship between the inorganic phosphate concentration in blood and the myocardial glucose extraction. It is likely that the elevated inorganic phosphate concentration in blood, as seen in patients with muscular dystrophy, is the key to the relationship between glycolysis and respiration.[29]

Wu and Racker,[30] studying the metabolism of ascites tumor cells in vitro, have found

Table 3

Myocardial Metabolism on Eleven Patients with Progressive Muscular Dystrophy

Patient	Cardiac index L./min./M.²	Coronary blood flow ml./min./100 Gm./LV	Myocardial O_2 extraction (Vol %)	Glucose (mg.%)		Pyruvate (mg.%)		Lactate (mg.%)		Malic dehydrogenase activity (units)		Aldolase activity (units)		Inorganic phosphate arterial blood concentration (mg. %)	Oxidation-reduction potential (Eh)* coronary A-V difference	Myocardial glucose oxygen extraction ratio %*
				Arterial blood concentration	Myocardial extraction	Arterial blood concentration	Myocardial extraction	Arterial blood concentration	Myocardial extraction	Arterial serum level	Coronary A-V difference	Arterial serum level	Coronary A-V difference			
R. J.	—	—	—	96	19.3	—	—	—	—	—	—	—	—	5.6	—	—
G. P.	5.4	92	12.3	58	8.3	.51	.13	6.07	.042	—	—	—	—	4.2	+3.0	50.3
F. D.	3.52	62	10.7	70.7	2.7	.281	.042	3.41	1.09	139	6	—	—	3.21	−3	19
R. Mc.	5.6	—	9.2	87.2	11.2	.246	.078	4.7	.16	266.6	0	83.3	0.0	4.24	+4.6	91
A. L.	—	—	12.2	100	16.0	.338	.180	7.80	3.11	200	8	116.5	6.5	5.48	+3.3	98.5
J. G. (rest)	5.15	82	10.3	86.2	10.6	.374	.046	4.44	−0.20	125	25	20	3.5	—	+2.3	78.3
J. G. (work)	5.3	76	9.2	98.6	11.0	—	—	—	—	110	35	17.5	−1.5	—	—	89.1
S. S.	5.0	—	12.2	87.8	12.6	.0908	.0403	4.33	1.76	—	—	27.5	−5	—	+1.0	77.3
L. F.	—	—	11.6	62.8	1.8	.181	−.024	4.79	1.82	220	90	20	3	—	−7.7	11.7
B. M.	—	—	8.7	76.8	6.2	—	—	—	—	40	−18	41	2.5	—	—	54
M. Z. (rest)	3.1	53	12.2	96.0	4	.414	.105	4.48	1.35	310	−30	—	—	3.48	−0.9	25.3
M. Z. (work)	4.2	80	13.2	91.5	10.5	.626	.303	9.2	.8	345	19	—	—	4.08	+7.6	59.5
L. D.	—	—	11.4	—	—	.456	.370	7.70	4.02	—	—	100	7	—	−7	—

*For explanation of calculation of per cent glucose oxygen extraction ratio and oxidation-reduction potential see text.

that increasing the extracellular concentration of inorganic phosphate resulted in its intracellular elevation. Fitch and Dinning[31] have demonstrated a high rate of turnover between extracellular and intracellular inorganic phosphate in vitamin E-deficient rabbits and rats. It has been shown repeatedly that an elevated intracellular inorganic phosphate concentration stimulates glycolysis.[30, 32–34] That this is possibly the case in patients with progressive muscular dystrophy is shown by the fact that an elevated concentration of blood inorganic phosphate is accompanied by increased myocardial glucose extraction (fig. 3), and that the increase in myocardial glucose extraction is directly related to an increase in glycolysis and heart muscle as shown in figure 1.

What is the mechanism of the elevation in the inorganic phosphate concentration in blood? It has been shown that either anaerobiosis or uncoupling of oxidative phosphorylation results in increased intracellular concentrations of inorganic phosphate with increase in the rate of glycolysis.[35] The data presented here show increased inorganic phosphate in blood along with aerobic glycolysis in heart muscle in the presence of a normal or slightly elevated myocardial oxygen extraction. This combination suggests uncoupling of oxidative phosphorylation. Further evidence of this is the finding of Danowski and co-workers[36] that children with progressive muscular dystrophy have an elevated basal metabolic rate and protein-bound iodine. The studies presented here also reveal an increased cardiac output (table 3). Experimental muscular dystrophy in vitamin E-deficient animals has been thought to be accompanied by uncoupling of oxidative phosphorylation.[37, 38] However, several investigators studying skeletal muscle in human progressive muscular dystrophy have concluded that the major metabolic defect in carbohydrate metabolism is a marked diminution of glycolysis.[39–41] These conclusions were based on the low intramuscular levels of certain glycolytic enzymes and the decreased

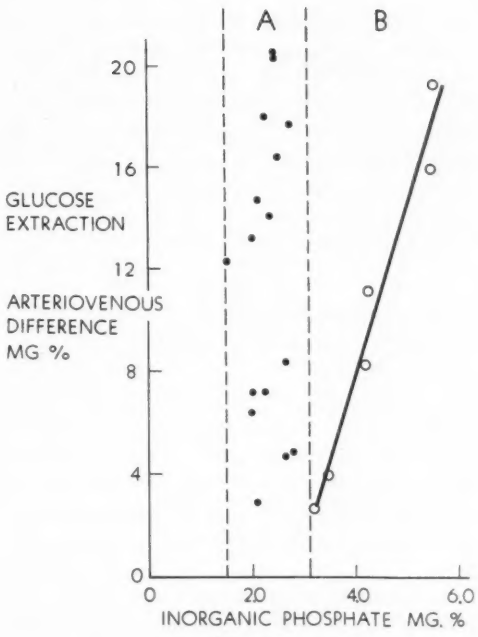

Figure 3

This shows the relationship between the arterial blood concentrations of inorganic phosphate and the myocardial glucose extraction. Section A shows the absence of correlation in patients with diseases other than muscular dystrophy such as hypertension, metastatic carcinoma, and low-output congestive heart failure. Section B shows that in patients with muscular dystrophy there is a linear relationship between the inorganic phosphate in blood and the myocardial glucose extraction.

lactate production by homogenates of dystrophic muscle.

The dangers and limitations of attempting to interpret the pathways of intermediary metabolism in the myocardial cell from the coronary arteriovenous differences of substrates are well appreciated.[42] From changes in the relationships between the concentrations of substrates in arterial and coronary sinus blood, however, certain tentative conclusions may be drawn. Thus, the relative increase in the ratio $\frac{La}{Py}$ between the arterial and coronary sinus blood reflects a similar change in the oxidation-reduction potential of

the heart muscle cell.[21, 22] Equally, the relationship between myocardial glucose extraction and the myocardial redox potential may provide information about the rate of glycolysis in heart muscle. Finally, the data obtained from arterial and coronary sinus blood have shown that an elevated inorganic phosphate concentration in blood increases rate of glycolysis in the myocardial cell.

Summary

Myocardial metabolism was studied in 11 patients with progressive muscular dystrophy. Coronary blood flow was measured in four, the cardiac output in six patients. The blood concentrations of oxygen, glucose, inorganic phosphate, pyruvate, and lactate, and the serum activities of malic dehydrogenase and aldolase were determined in simultaneously drawn coronary sinus and arterial blood samples.

The cardiac outputs were elevated in all patients. Myocardial extractions of pyruvate and lactate were negative in two patients. Inorganic phosphate concentrations in blood were elevated. Malic dehydrogenase and aldolase were released by the heart in several patients. Differences in oxidation-reduction potential between arterial and coronary venous blood were positive, suggesting glycolysis in the heart muscle. This was accompanied by increased myocardial extraction of glucose. Apparently aerobic glycolysis occurred, since sufficient oxygen was present to account for all glucose extracted.

Stimulation of glycolysis by inorganic phosphate was suggested by the relationship between the elevated inorganic phosphate concentration in blood and the myocardial glucose extraction. This suggests the possibility of uncoupling of oxidative phosphorlyation in the myocardium.

Acknowledgment

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Clinical, Pathologic, and Hemodynamic Considerations in Coarctation of the Aorta Associated with Ventricular Septal Defect

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IN COARCTATION of the aorta, the coexistence of a defect of the ventricular septum tends to prevent development of hypertension in the upper systemic circulation by permitting blood from the left ventricle to pass into the pulmonary circulation. This tendency is accentuated but not fundamentally altered if there is also a patent ductus arteriosus opening into the aorta proximal to the coarctation.

A more complicated situation obtains if the ductus enters the aorta distal to the coarctation. Then systolic pressure in the descending aorta tends to approach that in the pulmonary artery, owing to the equalizing effect of the ductus, and also the pressure in the ascending aorta may approach that in the pulmonary artery, owing to the equalizing effect of the ventricular septal defect. Consequently, little or no pressure gradient may exist across the coarctation. Recognition of the existence of coarctation in these circumstances is of great practical importance, as discussed later.

In this paper analysis is made of 26 cases of ventricular septal defect and coarctation of the aorta with or without patent ductus arteriosus, in which the diagnosis was fully established by pathologic, surgical, or complete hemodynamic data. Briefer reference, principally for purposes of classification, is made to 13 other cases in which this combination of defects formed part of more complicated malformations.

Classification According to Associated Abnormalities: In the classification used, the term "coarctation" includes all anatomic varieties of obstruction to the aortic arch—infolding of the aortic wall (usually referred to as coarctation) and also tubular hypoplasia, atresia of the isthmus of the aorta, and complete interruption of the aortic arch. In describing ventricular septal defects, the considerations elaborated by Becu and associates[1] will be followed; but for convenience, defects involving the region dorsal to the crista supraventricularis will be referred to as the "usual" type, those ventral to the crista as "high" defects, and those of the central part of the septum as "muscular" defects.

Cases of ventricular septal defect and coarctation of the aorta are most conveniently classified according to the additional malformations (table 1).

Cases with Normal Positions of Ascending Aorta and Pulmonary Artery

Isolated and with Proximal Patent Ductus Arteriosus

A ventricular septal defect tends to equalize pressures in the two ventricles during systole, and does so almost completely when the defect has an area greater than 1 sq. cm. per sq. m. of body surface.[2] Coexistent coarctation of the aorta increases resistance to emptying of the left ventricle and tends to direct more blood through the septal defect left-to-right (fig. 1, *left*). This reduces the hypertension in the aortic arch and its branches usually associated with coarctation. In consequence, an impression may be given that the aortic obstruction is mild when in reality it may be severe or even complete.

If there is also a patent ductus arteriosus opening proximal to the coarctation (fig. 1, *lower right*), the systemic and pulmonary cir-

From the Mayo Clinic and the Mayo Foundation, Rochester, Minnesota.

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Table 1

Classification in Ventricular Septal Defect Associated with Coarctation of Aorta

With normal positions of ascending aorta and pulmonary artery
Isolated ventricular septal defect with coarctation of aorta
With patent ductus arteriosus joining aorta proximal to coarctation
With patent ductus arteriosus joining aorta distal to coarctation
With subaortic stenosis and patent ductus joining aorta distal to coarctation
With abnormal positions of ascending aorta and pulmonary artery
Complete transposition
Corrected transposition
Origin of both great vessels from right ventricle
Truncus arteriosus

culations are in communication throughout the cardiac cycle and there tends to be an equalization of both systolic and diastolic pressures in the two circuits. This does not fundamentally alter the hemodynamics, however, and these two situations are considered together.

Table 2 gives data, including blood pressures as recorded by sphygmomanometer, from the seven cases of ventricular septal defect and coarctation of the aorta in which the ductus was closed and the five in which a patent ductus joined the aorta proximal to the coarctation.

Data on the anatomy of the aortic lesion were available in all cases, from either surgical or necropsy observation. In 10 the coarctation was of the usual type, causing severe obstruction in seven and mild in three; in the eleventh case the isthmus showed severe tubular hypoplasia; and in the remaining case the isthmus was represented only by a fibrous cord.

The anatomy of the ventricular septal defect was known in seven cases, among which the position of the defects was usual in three, muscular in two, and high in two.

The early clinical history in this group resembled that in any group of infants with large left-to-right shunts. Ten patients had recurrent respiratory difficulties in the first few months of life, variously diagnosed as pneumonia, "respiratory infection," or asthma. These difficulties were overcome with increase of age by all but one patient (case 1), who died when 3 months old. Other common handicaps were retardation of physical development and excessive fatigability.

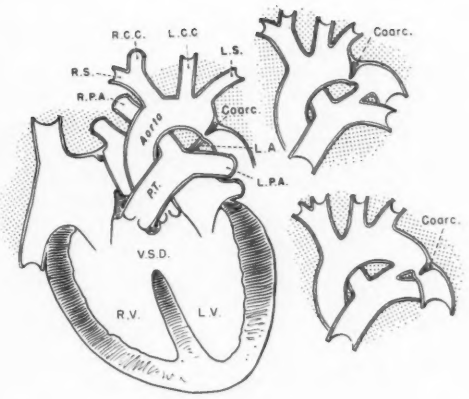

Figure 1

Left. *Ventricular septal defect with coarctation of aorta and obliterated ductus arteriosus.* Lower right. *Pulmonary artery and aorta in which a patent ductus joins the aorta proximal to a coarctation.* Upper right. *Pulmonary artery and aorta in which a patent ductus joins the aorta distal to a coarctation.*

On examination, a parasternal murmur from the ventricular septal defect was heard in each case. It was loud in all but case 10 (where severe pulmonary vascular obstruction with a small left-to-right shunt was present), and was accompanied by a thrill in about 80 per cent of the cases. Six patients also had an apical mid-diastolic murmur, but in none was a continuous murmur detected. In two cases the murmur was audible in the interscapular area; no case had clinically apparent collateral vessels.

Blood pressure in the arms was high normal or mildly elevated in nine patients. In the other three (cases 7, 9, and 11) the brachial pressure was more definitely elevated, as measured either clinically or by catheterization. In case 11 surgical exposure showed the ventricular septal defect to be small. In case 7

Table 2

Ventricular Septal Defect and Coarctation of Aorta, Isolated and with Proximal Patent Ductus Arteriosus: Clinicopathologic Data

Case	Sex	Age	Blood pressure in arms, mm. Hg	Blood pressure in legs, mm. Hg	Arterial pulsation in legs	Degree of coarctation (diameter)	Diameter of ductus	Area of VSD, cm.²	Area VSD, cm.² / Surface area, M.²
				Isolated VSD and Coarctation of Aorta					
1	M	3 mo.	*	*	*	Severe	—	—	—
2	F	22 mo.	125/75	80/?	Weak	Severe (3 mm.)	—	—	—
3	M	3 yr.	125/60	90/70	Absent	Severe (1.5 mm.)	—	0.3	0.5
4	M	4 yr.	140/80	80/60	Weak	Severe	—	0.8	1.33
5	M	7 yr.	134/80	Not recorded	Normal	Mild	—	0.8	0.9
6	M	8 yr.	125/68	80/?	Absent	Severe (2 mm.)	Minimal	—	—
7	M	11 yr.	150/110	Unobtainable	Weak	Complete	—	—	—
				With PDA Proximal to Coarctation					
8	F	6 yr.	120/80	125/90	Normal	Ductus acting as bypass	Narrow at pulmonary end	0.6	0.9
9	F	9 yr.	156/104	Unobtainable	Absent	Atresia	20 mm.	—	—
10	M	10 yr.	110/80	80/66	Weak	Severe (3 mm.)	4 mm.	—	—
11	F	16 yr.	140/80	Not recorded	Absent	Tubular hypoplasia (1 mm.)	Narrow	0.6	0.4
12	F	20 yr.	120/80	Not recorded	Normal	Mild (7 mm.)	Narrow	5.5	4.0

*Pressures unobtainable because of terminal status of patient when seen.

clinical examination and electrocardiography after repair of the coarctation indicated that the ventricular septal defect was small. In case 9 the pulmonary vascular resistance was so high that the ventricular shunt was right-to-left in spite of atresia of the aortic isthmus.

Lack of pulsation in the legs proved to be a reliable indication of severe coarctation. In the three instances of mild coarctation pulsation was normal, whereas it was diminished or absent in each of the other eight for which records are available.

Radiologic appearances were similar to those in cases of uncomplicated septal defect. Slight to moderate cardiac enlargement was indicated by the cardiothoracic ratio, the contours suggesting left ventricular enlargement in eight cases, right ventricular enlargement in two, and biventricular enlargement in two. Central pulmonary vessels were enlarged in all, with diminution of peripheral vessels in four. The aortic knob was small in 10 cases and normal in two. No case showed a double contour due to prominence of the left atrium. Notching of the ribs was minimal in four cases and absent in eight. In none was the coarctation visible.

On electrocardiographic examination the axis was normal or deviated rightward. The P waves indicated left atrial enlargement in six cases and right atrial enlargement in three, and were normal in three. The QRS complex was interpreted as showing hypertrophy of both ventricles in 11 and hypertrophy of the left ventricle in one. The initial vector was clockwise in six and counterclockwise in four, two cases having complete right bundle-branch block.

Hemodynamic studies were made of 10 patients—by cardiac catheterization in eight, and in two (3 and 4) by pressure measurements at operation (table 3). All but one had normal or mildly elevated arterial pressure in the upper part of the body. When coarctation was severe, the systolic pressure in the brachial (or radial) artery always exceeded the systolic pressure in the femoral artery. This relationship was not found in the three cases with mild obstruction of the aorta.

If the ventricular septal defect was less

Table 3

Ventricular Septal Defect and Coarctation of Aorta, Isolated and with Patent Ductus Proximal to Coarctation: Physiologic Data

Case	Blood oxygen saturation, per cent				Pressures, mm. Hg			Shunt, per cent	Resistance, dynes sec. cm.$^{-5}$	
	MV	RV	PA	Systemic artery	PA	Radial	Femoral		Pulmonary	Systemic
2*	53	64	64	96	55/30	110/55	80/40	L-R, 20	2300	5800
3	—	—	—	—	—	115/61†	88/64†	—	—	—
4	—	—	—	—	112/15‡	109/14‡	67/43‡	—	—	—
5*	72	85	87	97	42/7	120/87	116/77	L-R, 60	140	1900
6*	65	76	76	87	100/60	—	—	L-R, 50	—	—
8*	65	77	76	83	100/65	130/75	—	L-R, 65	800	2200
9	62	64	64	79	124/83	129/77	96/79	R-L, 30§	3200	2100
10 a*	72	78	78	93	112/60	113/64	64/56	L-R, 30	—	—
b	69	72	78	92	123/66	134/66	—	L-R, 40 R-L, 20	1200	1350
11	75	90	90	99	65/28	181/74	111/73	L-R, 60	250	1600
12	66	84	86	97	115/47	115/61	—	L-R, 60	650	1700

*Data from catheterization done elsewhere.

†From ascending and descending aorta at repair of coarctation.

‡From right and left ventricles and descending aorta at operation.

§Direction from dye curves.

Abbreviations: MV, mixed venous; PA, pulmonary artery; RV, right ventricle; —, not recorded.

Table 4

Ventricular Septal Defect, Coarctation of Aorta, and Distal Patent Ductus Arteriosus: Descriptions of Defects

Case	Source of anatomic detail	Ventricular septal defect		Coarctation of aorta		Patent ductus arteriosus
		Size	Location	Type	Size	
13	Necropsy	Small	Usual	Usual; prox. to left subclavian	—	Large
14	Necropsy	9 mm.	Usual	Tubular hypoplasia	—	Large
15	Necropsy	6 mm.	Usual	Interrupted arch	—	Large
16	Necropsy	6 mm.	Musc.	Tubular hypoplasia	2 mm.	Large
17	Necropsy	Small slits	Musc.	Tubular hypoplasia	1.5 mm.	Large
18	Necropsy	10 × 5 mm.	Musc.	Tubular hypoplasia	1 mm.	Large
19	Necropsy	10 × 3 mm.	Usual	Tubular hypoplasia	3 mm.	Narrow
20	Operation	?	?	Atretic isthmus	0	7 mm.
21	Operation	?	?	Atretic isthmus	0	6 mm.
22*	Necropsy	5 mm.	Musc.	Usual	2 mm.	2 mm.
23	Operation Necropsy		Musc. (and A-V commun.)	Usual	5 mm.	3 mm.
24	Operation	11 × 16 mm.	High defect extending posteriorly	Tubular hypoplasia	1 mm.	13 mm.
25	Catheter.					
26	Operation Necropsy	30 mm.	Musc.	Usual	0	Large

*Case 3 of Edwards and associates.[2]

Table 5

Ventricular Septal Defect, Coarctation of Aorta, and Distal Patent Ductus Arteriosus: Clinical Data

Case	Sex	Age at exam.	B.P., mm. Hg		Pulsation in legs	P2,* grade (1-4)	PSM,† grade (1-4)	Cyanosis	Course
			Arms	Legs					
13‡	M	12 hr.	—	—	—	—	—	—	CHF§
14	F	3 days	60′	—	0	2	2	Terminal	CHF
15‡	F	3 days	—	—	—	—	—	—	CHF
16‡	M	4 days	—	—	+ at birth 0 terminally		0	Terminal	CHF
17‡	F	10 days	—	—	—	—	+	Terminal	CHF
18‡	F	10 days	—	—	—	—	0	Terminal	CHF
19	F	3 mo.	100‖	60‖	0	—	3	—	CHF
20	M	8 mo.	100/60	100‖	Normal	2	3	0	Postop. death
21	M	10 mo.	120‖	60‖	0	2	3	0	Alive aged 4
22	F	23 mo.	90¶	—	—	+	+	Terminal	CHF
23	F	2 yr.	120/80	Not recorded	Normal	3	2	0	Postop. death
24	M	6 yr.	120/65	100/70	Normal	3	3	0	Alive aged 9
25	F	15 yr.	120/75	110/80	Normal	3	3	? toes	Alive aged 22
26	F	25 yr..	125/45	?	Normal	4	4	? toes	Postop. death

*Intensity of pulmonic valve closure.
†Parasternal systolic murmur.
‡Pressures unobtainable because of terminal status of patient when seen.
§Congestive heart failure.
‖Obtained by flush technic.
¶Systolic.

than 1 sq. cm. per sq. m. of body surface (cases 3, 5, 8, and 11), the pressure in the pulmonary artery was less than that in the ascending aorta. Such cases tended to have a somewhat higher arterial pressure above the coarctation than below. The cases with a larger defect had virtually identical systolic pressures in the aorta and pulmonary artery. Under these circumstances, the relationship between the diastolic pressures coincided with the direction of shunt, the pressure being lower in the pulmonary artery when the shunt was left-to-right and lower in the systemic artery in the one case where the dominant shunt was right-to-left.

With Distal Patent Ductus Arteriosus

The hemodynamic situation is strikingly altered if in addition to a large ventricular septal defect and coarctation a large patent ductus arteriosus joins the aorta beyond the obstruction (fig. 1, *upper right*). The septal defect tends to equalize the systolic pressure in the left and right ventricles, while the patent ductus tends to equalize pressures in the pulmonary artery and descending aorta. As a result there may be no significant pressure gradient across the coarctation.

In addition, the pulmonary artery blood may have an abnormally high oxygen content, owing to the left-to-right shunt through the ventricular septal defect; and this circumstance reduces the difference in oxygen saturation between aortic and pulmonary artery blood. Its consequence is minimization of the differential of cyanosis between upper and lower extremities, upon which clinical recog-

nition of right-to-left shunt through the ductus depends.

Fourteen proved cases with this combination of defects have been seen at the Mayo Clinic. Nine patients were females and five males. Four died during the first week of life, two in the second week, two more before the end of the first year, and two at 1 and 2 years of age. Three are still alive, now aged 4, 9, and 22 years; and one died following operation at age 25.

The chief pathologic features are summarized in table 4. In all cases the degree of aortic obstruction was severe, and in most the ductus was widely patent. Among the 11 in which the ventricular septal defect was examined, nine were large and two were small.

Clinical details were scanty in some of the cases ended by death in early infancy, but there are fully adequate data from seven cases and fairly adequate from two more (table 5).

Early respiratory difficulties occurred in 13 of these 14 cases, and eight of the patients died from congestive heart failure. Three other deaths occurred immediately following attempted surgical repair. Except as a terminal event, generalized cyanosis was not seen. Questionable cyanosis of the toes was observed in only the two oldest patients (cases 25 and 26), and none had unequivocal differential cyanosis. None had more than minimal elevation of arterial pressure in the arms. Pulsation in the legs was regarded as normal in five cases. In case 19, absence of femoral pulsation was associated with narrow patency of the ductus; and in case 21 (as discussed below), the shunt through the ductus was probably left-to-right, although the opening into the descending aorta lay beyond a completely atretic aortic isthmus.

The parasternal murmur of ventricular septal defect was loud in all patients surviving beyond infancy and was associated with moderate or marked accentuation of the pulmonary second sound. Five patients had also an early diastolic left parasternal murmur of pulmonary incompetence, and one had an apical mid-diastolic murmur; but in no case was a continuous murmur heard.

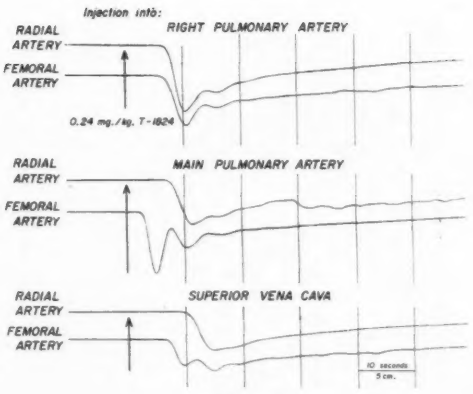

Figure 2

Case 25. Study of 19-year-old girl with ventricular septal defect, patent ductus arteriosus, and coarctation of aorta proximal to ductus. Demonstration by dye-dilution curves of a right-to-left shunt through the ductus and a coexisting left-to-right shunt through communication proved by oxygen saturation to be at the ventricular level. Following injection of dye into the right pulmonary artery, similar curves were obtained from radial and femoral arteries, indicating no shunt beyond that point. Following injection of dye into the main pulmonary artery, early-appearing dye was recorded at the femoral artery but not at the radial artery, indicating a right-to-left shunt beyond that point (patent ductus). Following injection of dye into the superior vena cava, early-appearing dye was again detected at the femoral artery but not at the radial artery, indicating no right-to-left ventricular shunt.

The derivation of some or all of the blood supply to the lower part of the body from the pulmonary artery increases the quantity of blood passing through the ventricular septal defect. Therefore, in patients with similar-sized ventricular defects, the systolic murmur tends to be louder in relation to the clinical evidence of severe pulmonary hypertension than it does in isolated ventricular septal defect with comparable pulmonary hypertension.

Thoracic roentgenograms were available in eight cases (numbers 16 and 20 to 26). All showed slight to moderate increase in transverse diameter of the heart. The pulmonary artery was prominent in seven, the central vessels were enlarged in all, and the periph-

Table 6

Ventricular Septal Defect, Coarctation of Aorta, and Distal Patent Ductus Arteriosus: Physiologic Data

Case	Age, yr.	Blood oxygen saturation, %					Pressures,* mm. Hg			Shunt, L-R, %	Dye Curves		Comment
		MV	RV	PA	Radial	Femoral	PA	Radial	Femoral		Injection	Sampling	
21	10 mo.	59	69	70	91	91	94/62	117/65	81/64†	35	SVC, RV, PA	Radial	All show moderate L-R shunt
24	6	59	67	65	90	65	113/76	147/70	113/75†	25	SVC, RV, RA	Radial Femoral	L-R only Always early-appearing
25 a	16	71	88	87	95	86	106/56	140/60	102/56‡	67	SVC, PA	Ear	L-R shunt
b	19	79	88	85	97	91	140/77	160/80	142/76‡	30	SVC, RV, PA, RPA	Radial, femoral	See fig. 3
26	25	76	92	93	98	91	114/61	136/59	134/57‡	75	From PA: at radial, L-R only; at femoral, R-L 40%. From RV: at radial, R-L 15%; at femoral, R-L 45%.		

*Each group of pressures recorded simultaneously.
†Pressure from descending aorta via catheter passed through ductus.
‡Pressure from needle in femoral artery.
SVC, superior vena cava; RPA, right pulmonary artery.

eral pulmonary vessels were enlarged in seven and diminished in one. The aortic knob was not defined in any, none showed notching of the ribs, and the coarctation was never visible roentgenographically.

Electrocardiograms were available in nine cases (numbers 14, 16, and 20 to 26). The axis was normal or deviated rightward in five, and deviated leftward in four. The P wave was normal in three. The QRS complexes showed biventricular enlargement in six, right ventricular enlargement in two, and left ventricular hypertrophy in one. The initial vector was clockwise in six and counterclockwise in three, including one patient whose ventricular septal defect was of the atrioventricular canal type and whose axis was –30°, with an RR′ pattern in V_1.

Full data from cardiac catheterization was available for four cases (21, 24, 25, and 26) (table 6). In case 21 the identity of oxygen saturation in radial artery and femoral artery blood excluded a large right-to-left shunt through the ductus; and the absence of additional arterialization in pulmonary artery blood made a large left-to-right flow through the ductus unlikely, although data obtained during breathing of oxygen suggested that the shunt tended to be in this direction. This evidence that the relatively small ductus in this case was not of great hemodynamic significance was supported by the presence of a pressure gradient across the coarctation, which in this case was specifically an atretic aortic isthmus.

In the three other cases there was a definite right-to-left shunt through the patent ductus. The diastolic pressure was similar in the pulmonary, radial, and femoral arteries. Systolic pressures in the right ventricle were closely similar to those in the pulmonary artery, but in each instance the systolic pressure recorded at the radial artery was considerably higher (+24 to +34 mm. Hg). As the systolic pressure in the left ventricle almost certainly was closely similar to that in the right, the higher systolic pressure at the radial artery probably represents the usual amplification of systolic pressure that occurs during transmission of

the arterial pulse to the periphery (Kroeker and Wood),[4] perhaps exaggerated by the comparatively small capacity of the vascular bed of the upper body.

Values for oxygen saturation at various sites in the right heart showed evidence of arterialization at the ventricular level in each case. The left-to-right ventricular shunt was small in case 24 but very large in cases 25 and 26. A right-to-left shunt through the ductus was demonstrated in each case, both by saturation data and by dye-dilution curves.

Figure 2 illustrates a typical group of dye-dilution curves taken from case 25. Following injection of dye into the right pulmonary artery, curves recorded from the radial and the femoral arteries demonstrated a left-to-right shunt only. When injection was made into the main pulmonary artery, however, a large right-to-left shunt was indicated by the curve recorded at the femoral artery but not by that recorded at the radial artery. When the injection was made into the superior vena cava, the curve from the radial artery again failed to show early-appearing dye, indicating that no right-to-left shunt was occurring via the ventricular septal defect. This indicated that the shunt through the ventricular septal defect was purely in the left-to-right direction and that the systemic vascular resistance in the upper body was higher than the resultant of the parallel resistances of the pulmonary vasculature and the resistance to blood flow to the lower body via the ductus. The large right-to-left shunt of approximately 50 per cent through the ductus suggested that the vascular resistance in the lower body was less than or similar to the pulmonary vascular resistance.

In the presence of both a ventricular septal defect and a patent ductus arteriosus one would expect the predominant shunt to be in the same direction through both defects, unless there is an obstruction to flow between the left ventricle and the site at which the ductus joins the aorta. If no such obstruction exists and if the pulmonary resistance is less than the systemic resistance, both shunts will be predominantly left-to-right. If pulmonary resistance is greater than systemic, both shunts will be predominantly right-to-left. Therefore the combination of a predominant left-to-right ventricular shunt and a predominant right-to-left shunt through the ductus must mean that an obstruction exists between the left ventricle and the point where the ductus joins the aorta. This obstruction could be at or below the aortic valve, but most often it is a coarctation of the aorta.

Recognition of the existence of coarctation by this indirect evidence is of great importance if the ventricular septal defect is to be repaired with use of extracorporeal circulation. In these circumstances, after ligation of the ductus the coarctation will hinder or prevent perfusion of the head or the lower body, depending upon the position of the perfusing arterial cannula.

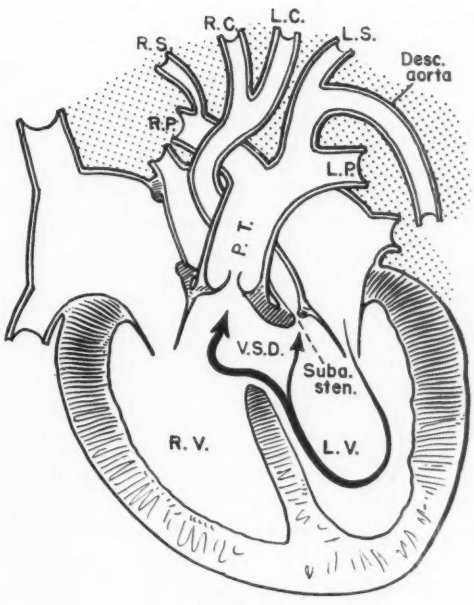

Figure 3

Subaortic stenosis associated with ventricular septal defect. The aortic arch is interrupted, and the descending aorta is continuous with a patent ductus. The left subclavian artery arises from the descending aorta and the right subclavian artery from the right pulmonary artery, being continuous with a right ductus.

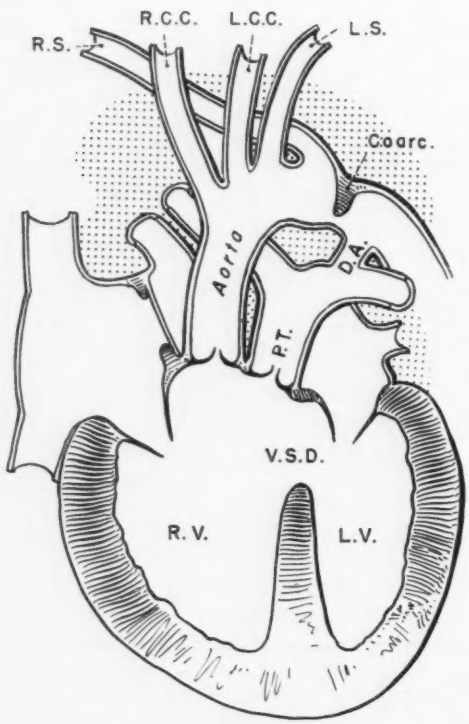

Figure 4

Both aorta and pulmonary artery arise from the right ventricle. The coarctation is proximal to a patent ductus. The origin of the right subclavian artery is anomalous, at it arises from the descending aorta distal to the left subclavian and proximal to the coarctation.

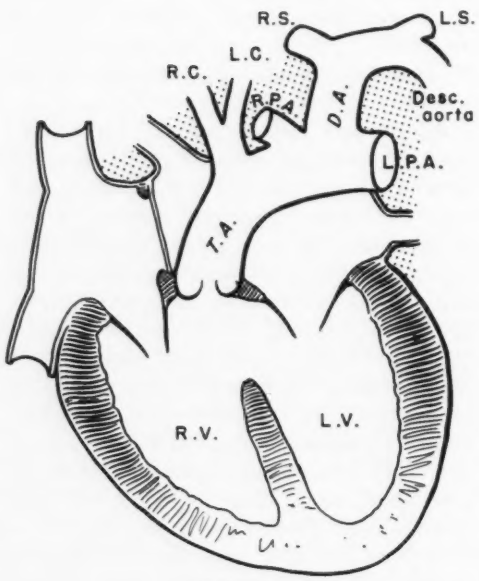

Figure 5

A single artery (truncus arteriosus) arises from the heart. Beyond the origin of the pulmonary artery the ductus continues into the descending aorta. There is no structure representing aorta between the origin of the common carotid arteries and the origin of the subclavian arteries from the descending aorta.

With Distal Patent Ductus Arteriosus and Subaortic Stenosis

The addition of subvalvular obstruction in the left ventricle (fig. 3) to the situation considered in the previous section increases the embarrassment of the circulation by directing more blood to the pulmonary circuit and lower body and making precarious the blood supply to the head and neck. Four cases in this category have been described in detail elsewhere;[5] and in all, seven examples now have been seen in this institution. In six of these, the ventricular septal defect was high, lying immediately below the pulmonary valve; and all had obstructive anomalies of the aortic arch and its branches in addition to subvalvular obstruction. The aortic valve was bicuspid in all seven cases.

Five of these patients died in the first 2 weeks of life, and the longest survival was 2 months. Most died in congestive heart failure; but one had a syncopal death, possibly related to inadequate cerebral perfusion.

Cases with Abnormal Positions of Ascending Aorta and Pulmonary Artery

Five patients, one an infant and four aged from 2 to 14 years, have presented with some form of transposition of the great vessels (fig. 4). These include a case described by Alcott and associates[6] as an example of the Taussig-Bing complex but which may be considered an example of complete transposition with the pulmonary trunk overriding a large ventricular septal defect. In each case, in addition to a defect of the ventricular septum and coarctation of the aorta, the ductus arteriosus was

patent and joined the aorta distal to the coarctation.

The predominant direction of blood flow through abnormal communications between the ventricles or between the great vessels is determined by the relative resistances of the available pathways, as noted in the previous section. If there are communications at ventricular and at arterial levels, shunting will be in the same direction at both sites unless there is additional resistance or obstruction to one pathway. A left-to-right shunt at one level associated with right-to-left shunt at the other implies the existence of coarctation or obstruction in the outflow tract, whatever the arrangement of the great vessels may be. When in this situation the aorta arises from the right ventricle to supply the upper part of the body, and the pulmonary artery arises from the left ventricle to supply the lungs and the lower part of the body, a higher oxygen saturation will be found in the arteries of the lower part of the body than in those of the head and arms. Another situation that can produce this phenomenon of reversed differential cyanosis is composed of transposition of the great vessels, patent ductus, and a pulmonary vascular resistance higher than the systemic resistance.

In corrected transposition of the great vessels, the aorta and pulmonary artery arise from their proper ventricles, although abnormally positioned. In itself, this abnormal position does not affect the hemodynamics, which instead are determined by the associated abnormalities in the same way as with normally positioned vessels.

Besides the five cases mentioned above, there was one example of persistent truncus arteriosus associated with interruption of the aortic arch (fig. 5). The patient was a female infant who died at 9 months of age. It was found that a single vessel emerged from the right ventricle and gave off a short branch that divided into right and left common carotid arteries. The main vessel then gave off two pulmonary arteries and continued as the ductus to the descending aorta, from which the subclavian arteries arose. Thus there was no structure representing the aorta between the origin of the common carotid arteries and the descending aorta.

It is noteworthy that there was no case in which coarctation of the aorta was associated with the tetralogy of Fallot.

Summary and Conclusions

The association of coarctation of the aorta with ventricular septal defect does not modify the accuracy of recognition of the septal defect. But the defect does provide an alternative pathway for the escape of blood from the left ventricle, thereby tending to minimize hypertension in the upper part of the body. Along with this, the radiologic evidence of coarctation is minimized or obscured and electrocardiographic changes resemble those in isolated ventricular septal defect. A substantial pressure gradient between upper and lower body, however, is a reliable indication of the existence of a severe degree of coarctation.

These considerations are not importantly affected by coexistence of a patent ductus arteriosus joining the aorta above the coarctation. Should a ductus join the aorta at the site of coarctation, it will either have the effect of bypassing the coarctation or will behave functionally as though it joined the aorta proximal or distal to the obstruction.

When in the presence of a ventricular septal defect and coarctation of the aorta a large patent ductus arteriosus joins the aorta beyond the coarctation, the pressure above and below the coarctation may be almost the same. The ventricular septal defect tends to equalize the systolic pressure in the two ventricles, so that the pressures in the pulmonary artery and descending aorta are very similar. The lower body may be supplied partially or completely by blood from the pulmonary artery. The oxygen saturation of blood in the pulmonary artery is abnormally high because of the shunt through the ventricular septal defect, and so the difference in oxygen saturation between the upper and lower body may be very small. In consequence, both the coarctation and the patent ductus may escape recognition on clinical grounds.

The demonstration at cardiac catheterization of a difference in arterial oxygen saturation between the upper and lower body and the confirmation by dye-dilution technics or angiocardiography of the coexistence of a left-to-right ventricular shunt and a right-to-left arterial shunt establish the presence of obstruction between the outflow tract of the left ventricle distal to the ventricular septal defect and the entry of the ductus into the aorta.

The hemodynamic situation produced when ventricular septal defect and coarctation of the aorta form part of more complicated combinations of defects is discussed briefly.

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Great Men

In the experimental sciences, great men are never the promoters of absolute and immutable truths. Each great man belongs to his time and can come only at his proper moment, in the sense that there is a necessary and ordered sequence in the appearance of scientific discoveries. Great men may be compared to torches shining at long intervals, to guide the advance of science. They light up their time, either by discovering unexpected and fertile phenomena which open up new paths and reveal unknown horizons, or by generalizing acquired scientific facts and disclosing truths which their predecessors had not perceived. If each great man makes the science which he vitalizes take a long step forward, he never presumes to fix its final boundaries, and he is necessarily destined to be outdistanced and left behind by the progress of successive generations. Great men have been compared to giants upon whose shoulders pygmies have climbed, who nevertheless see further than they.—Claude Bernard. *An Introduction to the Study of Experimental Medicine.* New York, The MacMillan Company, 1927, p. 42.

Arteriosclerotic Vascular Disease and Testicular Fibrosis

By FREDERIC G. DALLDORF, M.D.

THE PURPOSE of this paper is to report an interesting inverse relationship between arteriosclerotic vascular disease and advanced testicular fibrosis. In recent years increasing attention has been paid to the possible role of gonadal hormones in the pathogenesis of arteriosclerosis.[1, 2] It has long been suspected that high estrogen levels protect premenopausal women from the development of arteriosclerosis.[3, 4] More recently, evidence has been presented that suggests these hormones may play a similar role in men.[5] Progressive testicular fibrosis is a condition thought to occur more frequently in older men. Occasionally it is associated with a known cause (i.e., cirrhosis of the liver, long-term estrogen therapy), but in most cases its etiology remains obscure.[6-8]

Materials and Methods

The records of the Department of Pathology at the University of North Carolina School of Medicine contain completed protocols of 442 autopsies performed on men older than 35 years from January 1, 1955 through December 31, 1959. In order to study a more meaningful sample it was decided to exclude from this study all cases with known predisposing factors for or causes of either testicular fibrosis or vascular disease. The clinical summaries and autopsy protocols were reviewed and 185 cases were excluded at the start of the study for the following reasons: 112 patients had antemortem clinical diagnosis of hypertension; 24 patients had diabetes mellitus; 28 patients had cirrhosis of the liver; one patient had Marfan's syndrome; one patient had disseminated lupus erythematosus; one patient had tuberculosis of the testes; two patients had tumor tissue infiltrating the testes; one patient had had mumps orchitis; one patient had hemochromatosis involving the testes; two patients had received stilbestrol therapy for carcinoma of the prostate; one patient had previously undergone bilateral orchiectomy; in 10 cases the autopsies were limited; and the age of one patient was unknown.

The protocols of the remaining 257 cases were reviewed with special attention to the cause of death and the degree of arteriosclerosis in the coronary, cerebral, and systemic arteries and the aorta. All cases were classified into five groups according to the severity of arteriosclerotic vascular disease described. Group 1 consisted of those patients showing minimal atherosclerosis with only smooth yellow plaques in their elastic aortas and minimal or no intimal thickening of the cerebral and coronary arteries. Group 2 consisted of those patients showing moderate arteriosclerosis. Their aortas usually contained some calcified as well as yellow intimal plaques. Elasticity of the aorta was often still preserved to some degree and the coronary or cerebral arteries, or both, were only moderately narrowed. Group 3 consisted of those patients with severe arteriosclerotic disease of the aorta or cerebral or coronary arteries. Their aortas had poor elasticity and usually showed many gritty and roughened intimal plaques. The coronary and cerebral arteries were markedly narrowed and with many, often gritty, intimal plaques. Group 4 contained those patients who not only had severe arteriosclerosis of the aorta or coronary or cerebral arteries but who also showed definite lesions caused by this disease (i.e., myocardial or cerebral infarcts, peripheral arterial insufficiency with gangrene, arteriosclerotic aneurysms). Group 5 comprised those patients who died of arteriosclerotic vascular disease as a result of vascular insufficiency or hemorrhage from an arteriosclerotic vessel. All decisions regarding suitability of cases and degree of arteriosclerosis were made without knowledge of the testicular findings. The ages of the patients were recorded and the cases arranged in 5-year age groups (table 1).

The routine hematoxylin and eosin sections of the testes were obtained from the autopsy files. In the majority of cases a section of only one testis had been submitted. The testicular material was inadequate in 58 cases. The final sample was 199 patients.

Results

Histologic Findings

Many of the sections of testes in all age groups were essentially normal. The seminiferous tubules were large and lined by

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Table 1

Correlation between Testicular and Severity of Arteriosclerotic Vascular Disease

Age	Patients with normal or minimally fibrotic testes (155 Cases)	Patients with advanced testicular fibrosis (44 Cases)
96-100	5	
91-95		
86-90		
81-85	1	
76-80	5 4 3 3 3 3 2 2 2	4 3 2 2
71-75	5 5 5 5 5 5 5 5 4 3 3 3 2 2 2 2	5 4 4 1
66-70	5 5 5 5 4 4 3 3 3 3 2 2 2 2 2 1	3 3 2 1 1 1
61-65	5 5 5 5 5 5 5 5 5 4 4 4 4 3 3 3 3 2 2 2 1 1 1	3 2 1
56-60	5 5 5 4 3 3 3 3 3 3 2 2 1 1 1	3 3 3 2 1 1 1 1 1 1
51-55	5 5 5 5 3 3 3 2 2 2 2 1 1 1 1 1 1 1 1	3 2 2 2 1 1
46-50	5 5 5 4 2 2 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	2 2 1 1 1
41-45	5 4 2 2 1 1 1 1 1 1 1 1 1 1 1 1	2 2 1 1
36-40	5 5 2 1 1 1 1 1 1 1 1 1 1 1 1 1	1 1

Group 1, minimal atherosclerosis; 2, moderate arteriosclerosis; 3, marked arteriosclerosis; 4, marked arteriosclerosis with lesions due to vascular disease; 5, death due to arteriosclerotic vascular disease. Each group number represents one case.

active germinal epithelium. Their lumina contained mature sperm. The peritubular fibrous membranes were thin and delicate. There were occasional small clusters of a few Leydig cells scattered throughout the sections. In a few instances the Leydig cells were increased in number in an otherwise normal testis.

Other sections had changes that were interpreted as representing early atrophy and fibrosis. In some testes there was only diffuse minimal thickening of the peritubular fibrous membranes. In others there was diffuse atrophy of the germinal epithelium which was made up predominantly of Sertoli cells. In many sections a small percentage of the tubules was hyalinized, whereas the remaining tubules appeared normal or had only slight peritubular fibrosis. The Leydig cells were often increased in number in the sections with early fibrosis but this was not a constant finding. Atrophy of the germinal epithelium, minimal thickening of the peritubular fibrous membranes, or minimal focal hyalinization of the seminiferous tubules was not interpreted as being indicative of long-standing, progressive testicular fibrosis. The normal testes and those showing minimal changes were therefore considered together as one category.

Forty-four of the 199 cases had changes that were interpreted as representing advanced atrophy and fibrosis. Some testes showed marked, diffuse thickening of the peritubular fibrous membranes and widespread atrophy of the germinal epithelium. In a few instances extensive areas of hyalinized tubules were interspersed with clusters of large, normal-appearing seminiferous tubules. When one half or more of the tubules were hyalinized, those cases were arbitrarily placed with those of advanced diffuse fibrosis. The most severely involved organs showed almost complete hyalinization of all tubules with large aggregates of Leydig cells. The number of Leydig cells per microscopic field was usually increased in testes showing advanced fibrosis. In cases where sections of both testes were available (66 cases) and the degree of

fibrosis varied from one to the other (8 cases) the testis that was least involved was used for the final histologic classification.

Correlation between Severity of Arteriosclerotic Vascular Disease and Advanced Testicular Fibrosis

The results are presented in table 1. Of the 155 patients with normal or minimally fibrotic testes, 47 (30.3 per cent) had complications of arteriosclerotic vascular disease (groups 4 and 5), and 36 (23.2 per cent) died of those complications. Of the 44 patients with advanced testicular fibrosis, four (9.1 per cent) showed complications of arteriosclerotic vascular disease (groups 4 and 5) and only one (2.3 per cent) died of this disease. The incidence of complications of arteriosclerotic vascular disease (groups 4 and 5) among patients free of testicular fibrosis is significantly higher than the incidence of complications of arteriosclerotic vascular disease (groups 4 and 5) among those patients with advanced testicular fibrosis.

	groups 4 and 5	groups 1-3	
Normal testes	47	108	155
Fibrotic testes	4	40	44
	51	148	199

$\chi^2 = 7.04$; $0.01 > p > 0.005$.[9]

Since the only individuals in this study who are known to have had progressive arteriosclerotic vascular disease at the time of death are those who died of the disease (group 5), it is of interest that all but one of these 37 men (97 per cent) had little or no testicular fibrosis.

Discussion

The data presented here show a striking inverse relationship between arteriosclerotic vascular disease and idiopathic testicular fibrosis, but they do not explain the reason for this correlation. There are at least three possible explanations.

I. One possibility is that these conditions are related, as cause and effect. Perhaps older individuals with atrophic testes produce less androgenic hormones and these hormones in some way influence the development of arteriosclerosis. This does not seem likely. There is often an apparent increase in the number of Leydig cells associated with testicular fibrosis. The influence of androgens on the development of atherosclerosis has not been clearly demonstrated.[5, 10] Indeed, there is some evidence that they play no role at all.[11]

II. Another possible explanation is that the inverse relationship between testicular fibrosis and arteriosclerotic vascular disease is due to the patient's general state of nutrition. As can be seen in table 1, the individuals with advanced testicular fibrosis have a higher incidence of poor nutrition or cachexia, as described at autopsy, than do the individuals with minimal or no testicular fibrosis. It is also apparent that there are fewer obese patients, as described at autopsy, in the group with testicular fibrosis. If the general state of nutrition was the controlling factor in both conditions, then by studying a limited sample composed of patients who were described as being "well nourished" but not "obese," the observed correlation should no longer exist. These restrictions would bring the total sample to 124 cases, 20 with testicular fibrosis and 104 without. Of the 104 patients with normal or minimally fibrotic testes, 34 (32.7 per cent) had complications of arteriosclerotic disease (groups 4 and 5). Of the 20 patients with fibrotic testes, two (10 per cent) showed complications of arteriosclerotic disease (groups 4 and 5). Thus, the relative incidence of complications of arteriosclerotic vascular disease remains the same in both groups, even when the variable of general nutritional status is removed.

III. The last, and most attractive, hypothesis is that testicular fibrosis and the decreased incidence of arteriosclerotic vascular disease are separate manifestations of long-standing high levels of circulating estrogenic hormones. Many investigators believe that high levels of estrogenic hormones protect individuals from the development of arteriosclerosis. This was first observed in women[3, 4] and has more recently been demonstrated in men.[5] Men and women who are free of symptomatic arteriosclerotic vascular disease excrete greater amounts of biologically active estrogenic hor-

mones in their urine than do those individuals suffering from myocardial infarction. When large doses of estrogens are given to individuals suffering from arteriosclerotic vascular disease, the levels of blood cholesterol decrease and the levels of phospholipids rise.[12] Some investigators consider, however, that physiologic doses of these hormones have no influence on cholesterol or phospholipid blood levels.[13]

The association of testicular atrophy and advanced cirrhosis of the liver has long been recognized and is believed to be the result of prolonged exposure to high levels of circulating estrogens.[14] Patients who have been given long-term estrogen or stilbestrol therapy for carcinoma of the prostate or arteriosclerotic vascular disease develop progressive peritubular fibrosis and atrophy of the testes,[12, 15, 16]

These observations of others suggest that the phenomenon observed here is merely the result of the presence of a spontaneous high level of circulating estrogenic hormones. When an abnormal high level of estrogenic hormones persists for a long period of time, it may well arrest the development or progression of arteriosclerosis and at the same time produce progressive testicular fibrosis. It should be emphasized that not all cases of testicular fibrosis can be attributed to high levels of circulating estrogenic hormones. Patients who have testicular fibrosis and sterility associated with Klinefelter's syndrome evidently do not excrete excessive amounts of estrogenic hormones.[17, 18] Further direct studies are indicated before any conclusions can be reached.

Summary

The autopsy protocols and sections of the testes were examined in a group of 199 men over the age of 35 years who were free of known causes of either vascular disease or testicular fibrosis. In 44 (22 per cent) of the cases, testicular sections showed marked fibrosis of the peritubular membranes or complete hyalinization. Testes of the remaining men showed minimal or no signs of testicular fibrosis. Of these 155 patients with normal or minimally fibrotic testes, 47 (30.7 per cent) had complications of arteriosclerotic vascular disease (i.e., myocardial or cerebral infarcts, arteriosclerotic aneurysms, etc.) and in 36 cases (23.5 per cent) those complications were considered to be the cause of death. Of the 44 cases with advanced testicular fibrosis, four (9.1 per cent) had complications of arteriosclerotic vascular disease and only one patient (2.2 per cent) died of the disease. An interpretation of these findings is presented.

Acknowledgment

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Nature, Science and Understanding

I believe most simply in the nobility of this great effort to understand nature, and (understand) what we can of ourselves, that is science. I hope, less simply, that it may be a brave and worthy chapter of man's history to cope, with a full awareness of the frailty of his institutions, of his society, and of himself, with the new problems and new choices that this knowledge has opened. For, if we do not treasure the great inheritance on which all our work and life are based, and understand the radical novelty and the gravity of the situation in which we find ourselves, there will be few of our children to ask again of the need for new knowledge.—DR. ROBERT OPPENHEIMER. *The American Scientist,* Vol. 47, p. 212A, September 1959.

The Natural History of Isolated Ventricular Septal Defect

A Serial Physiologic Study

By Russell V. Lucas, Jr., M.D., Paul Adams, Jr., M.D., Ray C. Anderson, M.D., Nicolaas G. Meyne, M.D., C. Walton Lillehei, M.D., and Richard L. Varco, M.D.

THE ADVENT of curative surgery for the patient with ventricular septal defect has emphasized the need for a more precise knowledge of the natural history of this anomaly. Despite numerous studies in the last few years, many factors relating to the natural history of ventricular septal defects remain incompletely defined.

The diversity in clinical course of patients with isolated ventricular septal defect is particularly enigmatic. This problem has been partially clarified by clinical, physiologic, and pathologic studies by many workers, including Dammann and Ferencz[1] and Adams and associates,[2] who related the clinical symptomatology to the changes in the pulmonary vascular bed. Work by Edwards,[3] and Ferguson and associates,[4] and Wagenvoort[5] has more precisely defined the structural changes occurring in the lung subjected to the stress of increased flow and pressure. Understanding was further advanced by these workers through their assessment of the postnatal changes occurring in the pulmonary vascular tree in normal infants.[4-7]

A consideration of the hemodynamic consequences of an isolated ventricular septal defect should begin with a brief review of certain characteristics of fetal and neonatal circulatory systems. In the fetal state, pulmonary blood flow approximates only 10 per cent of the total cardiac output. Since pressures in the two ventricles are believed to be equal, the total pulmonary resistance must therefore substantially exceed the total systemic resistance.[8] At birth, total pulmonary resistance drops immediately and profoundly following expansion of the chest and replacement of the intra-alveolar fluid with air.[9] These mechanisms reduce the extramural pulmonary vascular pressure, permitting intramural pressure to distend the arterioles of the pulmonary vascular bed. This distention is largely responsible for the immediate fall in the total pulmonary resistance. To be sure, the neonatal pulmonary arteriole still characteristically possesses a marked degree of medial thickening.[6, 7]

Anatomic studies reveal that with time, and in the absence of cardiovascular anomalies, the prominent media of these thick-walled arterioles atrophies and the diameter of the lumina concomitantly increases. This transition is thought to be largely complete in the normal infant at 2 to 6 months of age.[6, 7] As a result of these anatomic changes (i.e., maturation), a further fall in total pulmonary resistance occurs. Studies by Wagenvoort and associates,[10] Ferguson et al.,[4] and Lucas and associates[11] suggest, however, that the maturation of the pulmonary vascular bed is not complete at 1 year, but continues through the first 4 years of life. The corresponding fall in total pulmonary resistance mirrors this histologic maturation of the pulmonary vascular bed during the period from birth through 4 years.[11]

An isolated ventricular septal defect imparts a stress, in the form of increased pulmonary arterial pressure and increased pulmonary blood flow, that may alter the normal

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Table 1

Incidence of Associated Defects

Isolated ventricular septal defect	40
Ventricular septal defect + coarctation of aorta	5
Ventricular septal defect + patent ductus arteriosus	7
Ventricular septal defect + corrected transposition	4
Ventricular septal defect + "acquired" pulmonary stenosis*	5
Ventricular septal defect + atrial septal defect	2
Multiple ventricular septal defects	1
Total	64

*The precise mechanism of this phenomenon of "acquired" pulmonary stenosis in ventricular septal defect is not known. Hence, these patients are considered separately, though they may represent yet another possible response in the patient with an isolated septal defect.

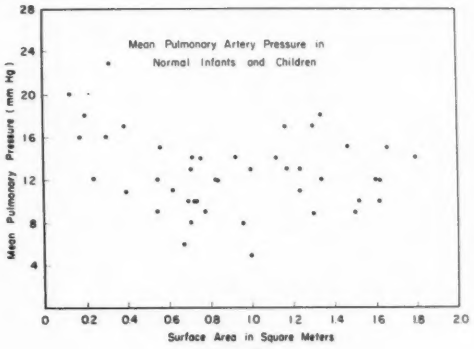

Figure 1

Mean pulmonary arterial pressure in normal infants and children. The mean value is about 12 mm. Hg and does not vary significantly with changing size. Use of age in place of surface area on the horizontal axis did not alter this grouping. (From Lucas et al.[11] Reproduced with permission).

maturation of the pulmonary vascular bed. Clinical and physiologic observations at many cardiac centers indicate the benignity of the *small* defect; hence we can conclude that the small lesion imposes minimal stress. But the effect on the primary vascular bed of a large ventricular septal defect, and the very definition of a "large" defect, are not so easily determined.

In the neonate with a "large" defect, the initial fall in pulmonary resistance allows massive pulmonary blood flow, and indeed many of these infants succumb from the resultant failure of the left ventricle.[12-15] Should the infant survive this critical period, his condition may spontaneously improve toward the end of the first year of life. Dammann and Ferencz,[1] on the basis of careful correlation of clinical, anatomic, and physiologic data, have demonstrated a stage of severe congestion followed by a period of relative absence of symptoms. After varying intervals, cyanosis developed in some of their patients. The pulmonary vascular bed, in the opinion of these authors, is responsible for this triad of clinical stages. They have concluded that the normal initial increase in the diameter of the pulmonary arteriole allows massive pulmonary blood flow and results in severe congestion. With time, anatomic alterations (medial hypertrophy and intimal proliferation) decrease the lumen of the pulmonary arteriole. The resultant decrease in the pulmonary blood flow brings about the period of relative freedom from symptoms. If the lumen diameter of the pulmonary arterioles decreases to the point at which pulmonary resistance exceeds systemic resistance, right-to-left shunting and cyanosis occur.

Only some patients progress through all three of these stages. As noted, many fail to survive the period of congestion. Others appear to maintain a high pulmonary resistance from birth, with early and persistent cyanosis. Edwards[3] has suggested that these patients have failed to achieve any normal maturation of their pulmonary arterioles. Occasional patients become cyanotic in later childhood without appreciable prodromal symptoms.

Alternative explanations have also been advanced for the spontaneous improvement in congestive symptoms seen in infancy. Gasul and associates[16] observed development of "acquired pulmonary stenosis" in patients with ventricular septal defect. It has been suggested[17, 18] that the relative size of the ventricular septal defect may decrease. These phenomena could, of course, allow clinical

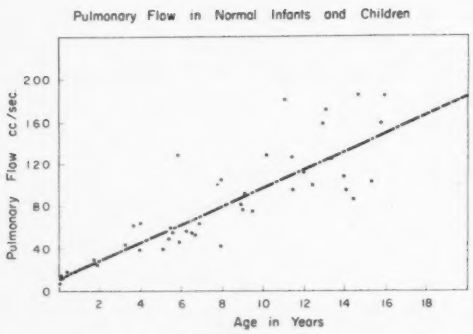

Figure 2

Pulmonary blood flow in normal infants and children in ml. per second. A gradual increase occurs with increasing age (From Lucas and associates.[11] Reproduced with permission.)

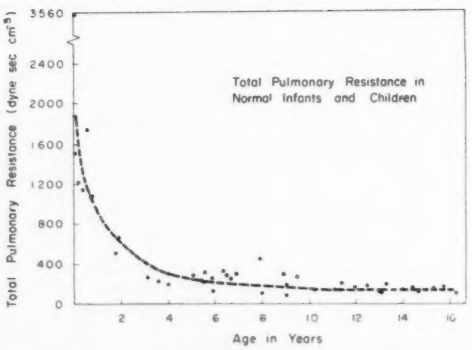

Figure 3

Total pulmonary resistance in normal infants and children. Note the rapid decrease in total pulmonary resistance in the first 2 years and achievement of essentially "normal" adult values at about 4 years of age. (From Lucas and associates.[11] Reproduced with permission).

improvement without a change in the pulmonary vascular bed. The variety of clinical courses, and the different theories advanced to explain these variations have led to conflicting opinions about the natural history and treatment of isolated ventricular septal defect.

This report attempts through serial studies to define the physiologic courses followed by a group of patients with isolated ventricular septal defects.

Material and Methods

Table 1 lists the cardiac defects present in 64 patients who underwent two or more physiologic studies prior to surgical intervention. This report is limited to the 40 patients who gave evidence only of isolated ventricular septal defect. To eliminate complicating variables we have excluded from consideration the other 24 patients who presented a variety of cardiac anomalies in addition to this defect. The age of the patients with isolated ventricular septal defect at the time of right-sided heart catheterization ranged from 3 months to 16 years. The interval between catheterizations varied from 6 months to 7½ years. All catheterizations at the University of Minnesota were performed without premedication and with local anesthesia only. Pressures were obtained by means of the Statham strain-gage model no. P23G and were electronically integrated. Oxygen determinations were performed by the method of Van Slyke.

In patients older than 5 years of age oxygen consumption was measured by means of a Benedict-Roth spirometer. In younger patients, the oxygen consumption was calculated by an assumed basal value of 172 ml. of oxygen per square meter per minute. Pulmonary blood flow was computed with the Fick principle, and total pulmonary resistance was calculated as follows:

$$\text{TPR} = \frac{\text{mean pulm. pressure in mm. Hg} \times 1332}{\text{pulmonary flow in ml. per second}}$$

Thirty-two of the patients with isolated ventricular septal defect have undergone operation for complete surgical correction of the anomaly. In nine of these patients at autopsy, and for the remainder at the time of operation, the location and size of each defect were carefully noted. In the eight remaining cases, the diagnosis of isolated ventricular septal defect has not been confirmed surgically or at necropsy.

Heart catheterization was performed in nine patients at a postoperative interval of 7 to 24 months, with an average of 13 months.

Values for total pulmonary resistance, pulmonary blood flow, and pulmonary pressure obtained from catheterization studies on normal infants and children are shown in figures 1 to 3.[11] These values, which appear also in subsequent figures as points of reference, form the basis of the physiologic groupings devised for these patients with isolated ventricular septal defect.

Results

The patients with isolated ventricular septal defect have been grouped initially according to the level of total pulmonary resistance at each catheterization. They have been di-

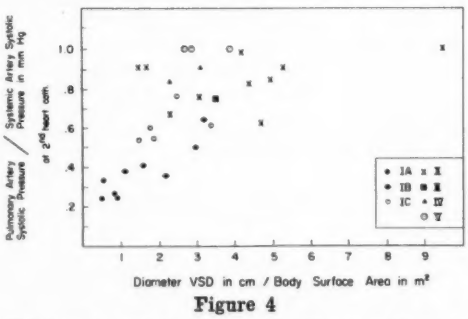

Figure 4

Relation of defect size to the ratio of pulmonary and systemic systolic pressures. In general, the larger the defect, the greater the ratio of pulmonary to systemic pressure. Those patients with defects measuring less than 1 cm. per M.² of body surface area have the lowest ratio of pressure, and all fall in group IA. When the defect size is greater than 1 cm. per M.² of body surface area, the pressure ratio appears almost independent of defect size. The physiologic group into which the patient falls also appears to depend on other factors than size, once the defect is greater than 1 cm. per M.² of body surface area.

vided further on the basis of pulmonary flow and pressure. These classifications are shown in table 2.

In figure 4, the ratio of systolic pulmonary arterial pressure to systolic systemic pressure has been plotted against the diameter of the defect per square meter of body surface area.* A general correlation exists between relative defect size and relative pulmonary arterial pressure. Among patients in group 1A (normal total pulmonary resistance, low flow and pressure) each defect was less than 1 cm. in diameter per M.² of body surface area, and the systolic pulmonary arterial pressure ratio was less than 0.33. All patients with the defect greater than 1 cm. per M.² of body surface area had a higher systolic pressure ratio, but the magnitude of the defect beyond this point did not relate precisely to the pressure ratio. Likewise, the variable physiologic responses among the patients with defect size greater than 1 cm. per M.² of body surface

*One patient (case 40) had a defect in the muscular septum; all other defects were located in or near the membranous septum.

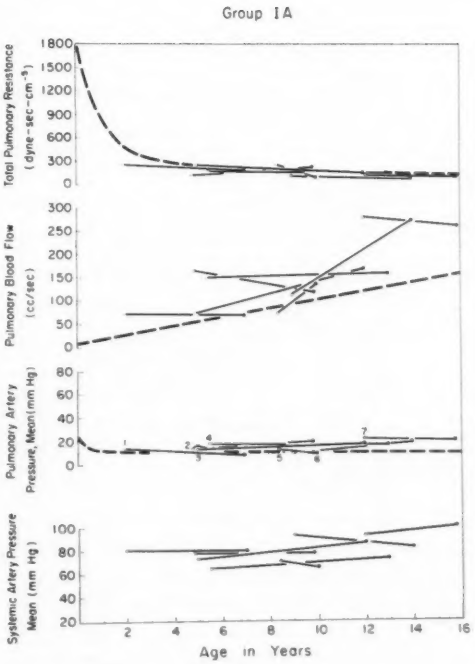

Figure 5

Group IA. The broken lines in this and subsequent figures represent the normal values depicted in figures 1 to 3. The open dot represents the first right-sided heart catheterization, and the closed dot indicates the second procedure. The case numbers are placed near the initial open dot. The patients in this group, with one exception, were older than 5 years when first studied. Total pulmonary resistance was normal for age at each study. Pulmonary blood flow was moderately elevated, and its increase roughly paralleled the expected normal increase with age. The mean pulmonary arterial pressure was minimally elevated and did not increase with age.

area suggested that factors other than ventricular septal defect size alone were operative.

Group IA. Normal Pulmonary Vascular Maturation. Small Ventricular Septal Defect. Minimal Physiologic Abnormality

Figure 5 summarizes the physiologic data relating to these seven patients. The total pulmonary resistance at each catheterization study was at the normal level. The absolute pulmonary flow was slightly elevated and paralleled roughly the expected increase with

Table 2

Summary of Classification of Isolated Ventricular Septal Defect

Group I	Normal pulmonary vascular maturation (normal fall in total pulmonary resistance with age) IA Small ventricular septal defect (less than 1 cm./M.^{2}) IB Apparent decrease in relative size of ventricular septal defect IC Large ventricular septal defect
Group II	Delayed maturation of pulmonary vascular bed (delayed fall in total pulmonary resistance) Large ventricular septal defect
Group III	Failure of pulmonary vascular maturation (no fall in total pulmonary resistance from fetal level) Large ventricular septal defect
Group IV	Normal or delayed maturation of pulmonary vascular bed followed by evidence of progressive pulmonary vascular changes. (Increasing total pulmonary resistance after normal or nearly normal decrease from the fetal level) Large ventricular septal defect
Group V	Cyanotic patients. Pathway to high pulmonary vascular resistance unknown Large ventricular septal defect

age. The mean pulmonary arterial pressure was only slightly elevated (under 25 mm. Hg) and did not increase with time. As shown in figure 4, the defect size was less than 1 cm. per M.^{2} of body surface area in each of the four patients in whom the defect was measured at the time of operation. The average age of these patients was 6 years at the first catheterization and 11.6 years at the second.

Wood[20] has suggested that a ventricular septal defect larger than 1 cm. per M.^{2} of body surface area can allow a common ventricular ejectile force to the pulmonary trunk and aorta. The defect size in this group lends support to this approximate value as the critical orifice area below which abnormal physiologic responses are minimal. The clinical course followed by these patients, who had virtually no symptoms and essentially normal thoracic roentgenograms and electrocardiograms, was compatible with the nearly normal physiologic values.

The normality of total pulmonary resistance in this group of patients at each study suggests that the pulmonary vascular bed had achieved normal maturation. No progressive vascular changes developed during the period of observation.

One patient (case 6) had had a bacteriologically proved (*Streptococcus viridans*) subacute bacterial endocarditis that was successfully treated medically. At operation 3 years later, the severe scarring observed in the septal leaflet of the tricuspid valve required plastic repair. While these patients exhibit minimal physiologic changes, their cardiac malformations cannot be considered completely benign.

Group IB. Normal Pulmonary Vascular Maturation. Large Ventricular Septal Defect. Apparent Decrease in Relative Size of Defect

These five patients (fig. 6) underwent initial catheterizations before 1 year of age. The total pulmonary resistance fell along the normally expected path. Pulmonary flow was moderately elevated. The mean pulmonary arterial pressures initially were considerably above the level seen in group IA, but at the time of the second study they had decreased in four of the five patients. This pressure drop without concomitant fall in the systemic pressure was noted in only two other patients in our series (group III).

Figure 7 is representative of the ratio of systolic pulmonary arterial pressure to systolic systemic pressure at each catheterization of the patients in group IB. This fraction, we believe, indicates the degree of communication between the two ventricles. Hence the fall in this ratio noted in all cases suggests decrease in the relative size of the ventricular communication.

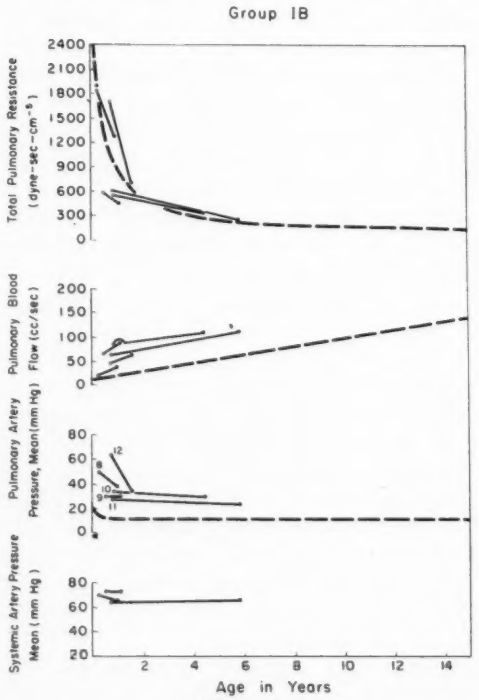

Figure 6

Group IB. All five of these patients were under 1 year of age during the first physiologic study. Total pulmonary resistance had fallen along the normal expected pathway. The mean pulmonary artery pressure had fallen sharply in two patients and slightly in two more. This pressure change is further amplified in figure 7.

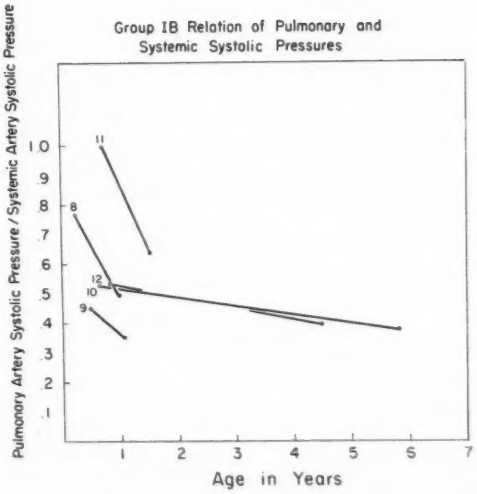

Figure 7

Relation of pulmonary and systemic systolic pressure in group IB. A decrease in the ratio of the pulmonary arterial to systemic arterial systolic pressure was seen in all patients; this suggests a decrease in the relative size of the ventricular septal defect.

Three of these five patients showed symptoms from infancy onward, with frequent severe respiratory infections, pneumonia, and growth failure. Two patients (cases 9 and 11) were operated upon at 13 and 19 months, respectively. A third patient (case 10) spontaneously improved at age 2 and remained symptom-free; she was operated on at age 5. The remaining two patients (cases 8 and 12) had minimal symptoms.

Fall of the total pulmonary resistance in these patients along the curve followed by normal patients suggests that normal maturation of the pulmonary vascular bed was achieved. The fall in the ratio of pulmonary arterial systolic pressure to systemic systolic pressure supports the hypothesis of a decrease in the relative size of the ventricular septal defect. If the defect size had been unchanged, a decrease in total pulmonary resistance unaccompanied by a decrease in systemic resistance would have allowed an increase in pulmonary blood flow (left-to-right shunt). This increase did not occur in these patients. It is noteworthy that despite this presumed decrease in size, all defects were still larger than 1 cm. per M.^{2} of body surface area at the time of surgical intervention.

Group IC. Normal Pulmonary Vascular Maturation Despite High Pulmonary Blood Flow and Elevated Pulmonary Arterial Pressure. Large Ventricular Septal Defect

The total pulmonary resistance of these five patients (fig. 8) was at the normal level for the age at each study. The absolute pulmonary blood flow, however, was greatly elevated. The mean pulmonary arterial pressure was moderately elevated and did not change appreciably during the interval between studies. In each of these cases (fig. 4) the diameter

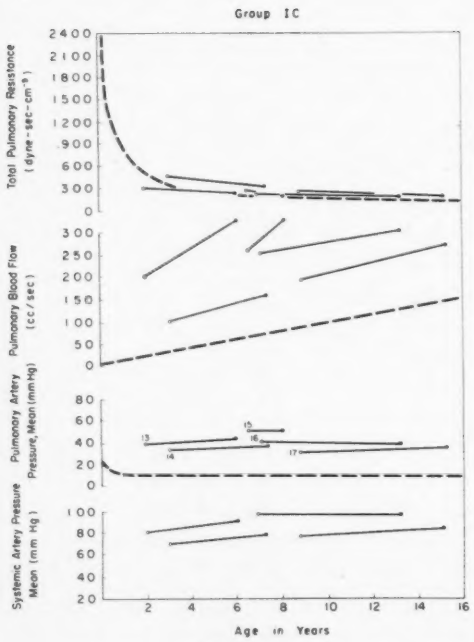

Figure 8

Group IC. Total pulmonary resistance in these patients was normal. The pulmonary blood flow was very high. Mean pulmonary artery pressure was moderately elevated. Despite this high flow and elevated pressure, no increase was seen in either the total pulmonary resistance or mean pulmonary pressure.

of the ventricular septal defect was between 1.5 and 3.5 cm. per M.^{2} of body surface area. Each patient in this group had a ratio of systolic pulmonary arterial pressure to systolic systemic arterial pressure that was greater than 0.5.

Clinically, four of these five patients (cases 13 to 16) were severely handicapped by frequent respiratory infections, pneumonia, and congestive heart failure. These problems persisted until operations were performed when the patients were 9 to 13 years of age.

Each patient in this group had a large ventricular septal defect and apparently normal maturation of the pulmonary vascular bed; as a consequence, elevated right ventricular pressure was maintained in each case by means of an exceedingly high pulmonary blood flow (hyperkinetic pulmonary hypertension). Despite these cardiac stresses persisting over several years, none of these patients exhibited pulmonary changes tending to limit such a volume, although four of the five had severe symptoms.

We regard the normality of pulmonary vascular maturation in this group of patients as unique, since patients in subsequent groups with apparently similar stresses followed quite different courses.

Group II. Delayed Maturation of the Pulmonary Vascular Bed. Large Ventricular Septal Defect

These 10 patients (fig. 9) evidenced delayed fall in total pulmonary resistance, with an approximation of normal levels during the interval between the two catheterizations. Pulmonary blood flow approached normal value for age at the first study, and it had increased to levels considerably above the normal value for age by the second study. Three patients showed rises in mean pulmonary arterial pressure without comparable rises in mean systemic pressures.

Six of these patients had rather large defects, the diameter measuring more than 4 cm. per M.^{2} of body surface area. In no other group of patients were defects of this relative magnitude observed. Nine patients exhibited symptoms of moderate congestion and growth failure; the exception was the patient with the smallest defect (case 26). None was cyanotic. These patients' ages covered the entire childhood span (6 months to 12 years) at the time of the first catheterization.

The fall in total pulmonary resistance in these patients occurred later and with a more gradual slope than the fall seen in normal infants; this suggested a delay in the normal maturation of the pulmonary vasculature. Since normal maturation was the first initial response of the lung to the stress of a large ventricular septal defect, this group illustrates the effects of a second initial response. Although six patients had very large defects, among the total group (fig. 4) defect size does not appear to have been primarily responsible for this difference. Since we know of no other factors that might bring about this delay of pulmonary vascular maturation, we continue to hold that inherent differences in the vas-

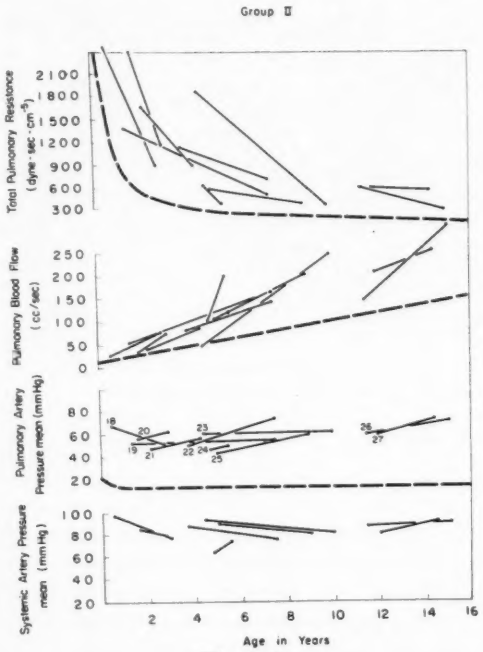

Figure 9

Group II. In these patients the normally expected decrease in total pulmonary resistance was delayed. Pulmonary blood flow increased beyond normal levels. Despite the fall in total pulmonary resistance, the mean pulmonary pressure remained stable or increased slightly in nine of the 10 patients.

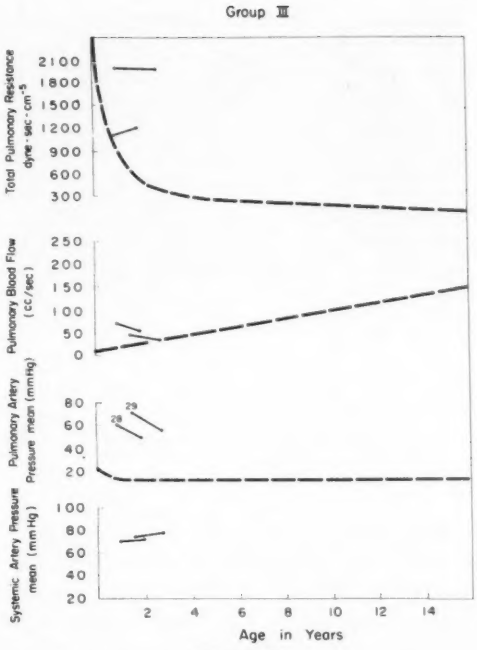

Figure 10

Group III. The total pulmonary resistance in these two young infants did not change from the initial high values. A decrease in mean pulmonary artery pressure occurred. These patients may possibly represent an early stage prior to a delayed fall in resistance as seen in group II. They might also reach the end state depicted in group V (fig. 13).

cular bed may be responsible for the apparent differences in response to similar stress.

Defect size did appear, however, to influence surgical mortality. Surgical correction had been attempted in all 10 of these patients. Five of them died within 48 hours, apparently from failure of the left side of the heart; four of these fatalities occurred in patients with very large ventricular septal defects, in at least two of which the size of the defect was definitely a contributory factor. In one (case 22) the membranous septum was virtually absent, and the sutures had pulled out at the superior margin of the patch; in the other (case 24) the large Ivalon patch used in the repair buckled and partially occluded blood flow to both the pulmonary artery and aorta. No specific cause of death was determined in the other three cases.

Group III. Failure of Pulmonary Vascular Maturation. Large Ventricular Septal Defect

In two patients (fig. 10) total pulmonary resistance did not fall significantly below the fetal level with the lapse of time. The absolute pulmonary blood flow remained low and did not increase with age, and when computed on the basis of square meters of body area, it decreased. The mean pulmonary pressure fell in both patients, as did the ratio of systolic pulmonary arterial pressure to systolic systemic arterial pressure. The one defect measured was quite large (3.5 cm. per M.^{2} of body surface area). Both patients had severe symptoms (recurrent pneumonia and congestive heart failure) in infancy. They improved somewhat in the interval between studies, but because of the persistent high total pulmonary

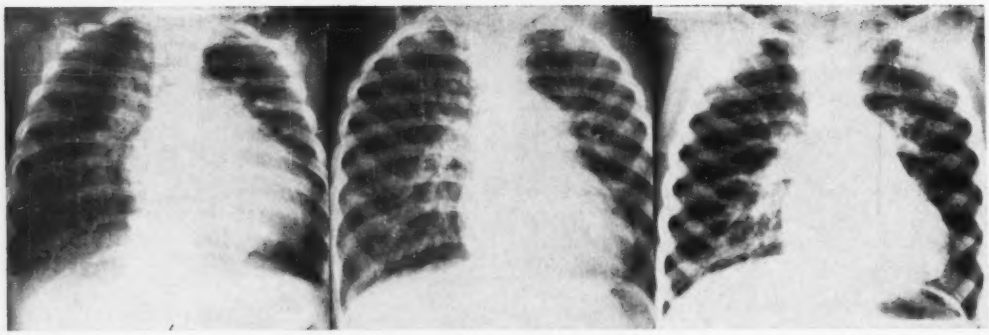

Figure 11

Six-foot posteroanterior roentgenograms in case 29, group III. Left, age 6 months. Center, age 2 years. Right, age 4 years. Normal peripheral pulmonary vascular markings and increased proximal markings. The other patient in group III had similar roentgenograms.

resistance, they were treated surgically. Both survived operation and later showed moderate improvement clinically. The roentgenograms in these patients were of unusual interest in that normal peripheral pulmonary markings were associated with a pronounced increase in the proximal vascularity at the earliest roentgenographic examination, and the disparity in the pulmonary markings persisted to the time of operation (fig. 11).

These two patients with large ventricular septal defects appear to have achieved little or no maturation of the pulmonary vasculature. The maintenance of the total pulmonary resistance at or above fetal levels, and the absolute limitation of the pulmonary blood flow support this thesis. This pattern, then, constitutes a third type of initial response of the pulmonary vascular bed in a patient with a large ventricular septal defect. One may legitimately ask, however, if these patients would show a subsequent fall in total pulmonary resistance similar to that demonstrated in group II. Another potential pathway available to these patients is seen in group V, in which three cyanotic older patients with initial total pulmonary resistance above fetal levels showed the following pattern: continuing increases in total pulmonary resistance; increasing pulmonary arterial pressure; and pulmonary blood flow of less than 50 ml. per second. This pattern is precisely what might be anticipated if failure of pulmonary vascular maturation occurred and persisted to this older age. It is impossible to ascertain which course these patients in group III might have followed without surgical intervention.

Group IV. Apparent Normal Pulmonary Vascular Maturation Followed by Progressive Pulmonary Vascular Changes. Large Ventricular Septal Defect

Figure 12 summarizes studies on four patients whose total pulmonary resistance initially fell to nearly normal values. This initial drop was followed by an increase in total pulmonary resistance. For case 31 this was precisely revealed during the course of three cardiac catheterizations. In the other three patients the fall was assumed, and significant increases in total pulmonary resistance were demonstrated in a later examination. The wide variation in age at which the total pulmonary resistance rose among patients in this group (6 months to 11½ years) is of interest. The mean pulmonary artery pressure increased in three patients and decreased slightly in one, but these changes in the mean pulmonary pressure were associated with comparable changes in the mean systemic pressure.

All four patients in the group had symptoms of severe congestion during infancy. For one of them (case 30) these symptoms were interrupted by an operation at age 18 months. The other three showed a dramatic "spontaneous" improvement in symptoms of

congestion during the period of observation. Cyanosis developed in two of them subsequent to this clinical change (cases 31 and 33); since they were then considered operable only at an enhanced risk, they were not referred for surgical correction of their defect.

These patients represent a group in which maturation of the pulmonary vascular bed proceeds in a normal or nearly normal fashion. This process is then interrupted (at varying ages) by a progressive rise in the total pulmonary resistance. The two cyanotic patients have followed the clinical pattern suggested by Dammann and Ferencz.[1] The physiologic data support their hypothesis that this clinical course is secondary to pulmonary vascular changes.

The marked disparity in the ages at which the various stages of disease were manifested suggest a complex etiology and renders precise prognosis difficult.

Group V. High Pulmonary Vascular Resistance and Cyanosis. Large Ventricular Septal Defect

The seven patients in this group (fig. 13) all gave evidence of cyanosis before the initial studies were made. Therefore, the data have not been very helpful in explaining the etiology and development of cyanosis in these persons with ventricular septal defect. We have included them in order to describe better the course of this affliction once cyanosis has taken place. They ranged in age from 3½ to 9 years when first seen by us. These cyanotic patients can be separated into two groups on the basis of the initially measured total pulmonary resistance and the response of the total pulmonary resistance with time:

A. Patients with Initially High Pulmonary Resistance that Continued to Rise

These were all obviously cyanotic when first seen by us (cases 34, 35, and 36). The onset of cyanosis was 6 weeks, 6 years, and 10 years, respectively. Total pulmonary resistance in these three patients significantly increased over time. In these cases the absolute pulmonary blood flow was limited to about 50 ml. per second, despite differences in size and age. (Limitation of pulmonary blood flow to this level was noted in the two patients in group III who achieved no pulmonary vascular maturation.) All had moderate exertional dyspnea and growth retardation, but were otherwise without symptoms. They were considered to represent substantially increased operative risks and therefore were not referred for surgical correction. Anatomic confirmation of the diagnosis of ventricular septal defect has not been made in these patients. Some may actually represent a different congenital anomaly. We have included them because these cases suggest a potential course followed by patients with failure of pulmonary vascular maturation.

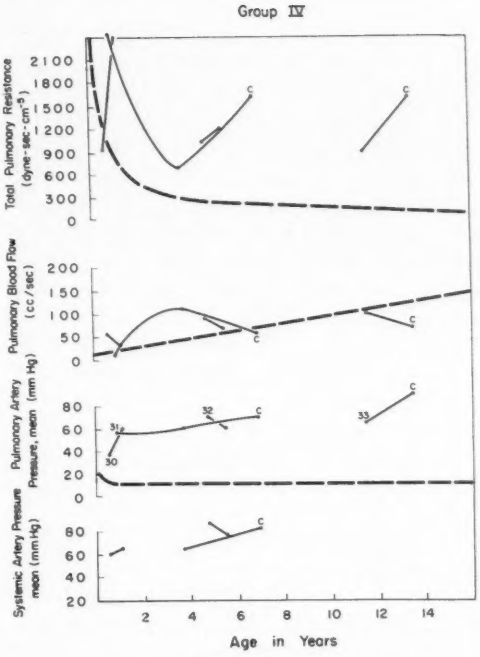

Figure 12

Group IV. C indicates cyanosis. In case 31 a fall in total pulmonary resistance was followed by a rise during the course of three catheterization studies. In the other three patients, if a normal fall is assumed from the normal neonatal value to the value at the first study, this same course was followed. The age of onset of the rise in total pulmonary resistance varied widely.

B. Patients with Lesser Initial Pulmonary Resistance and with a Slight Decline in This Value Occurring with Growth

In these four patients (cases 37 to 40) the

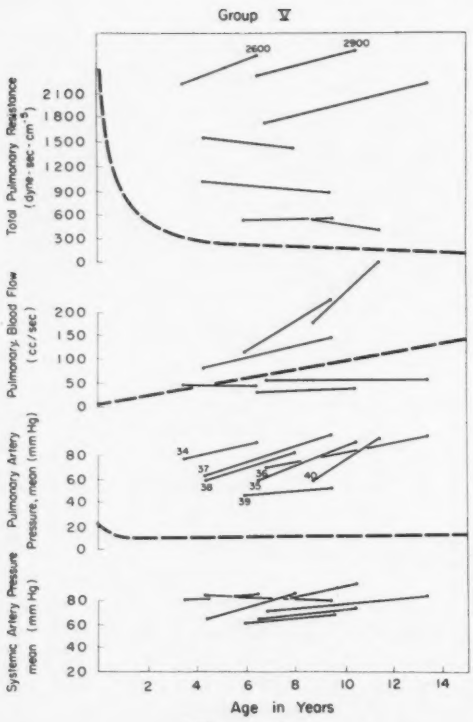

Figure 13

Group V. These patients were cyanotic prior to the first heart catheterization. The three patients (cases 34, 36, 39) with the high and rising total pulmonary resistance had fixed, abnormally low pulmonary blood flows and rising pulmonary pressures. The other patients, while cyanotic, showed no increase in the total pulmonary resistance and had abnormally high pulmonary flows.

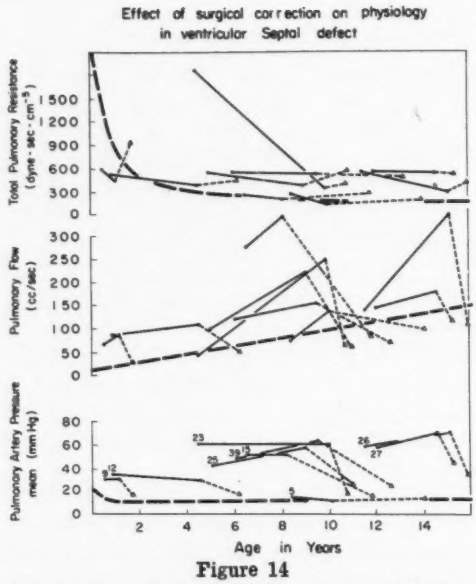

Figure 14

Effect of surgical correction on the physiology in ventricular septal defects. The open dot represents the first preoperative study and the closed dot, the second preoperative study. The open triangle represents the postoperative study. The broken line then represents the postoperative change. In all patients the postoperative pulmonary blood flow fell to normal or slightly below normal levels and the mean pulmonary arterial pressure dropped significantly to normal or near normal values. In case 9 the total pulmonary resistance increased, but in all others did not change appreciably during the year following surgical intervention.

pulmonary blood flow was somewhat above normal and increased slightly. Thus, each had a small left-to-right shunt in addition to the right-to-left flow. Pulmonary arterial pressures in these patients increased with age. These four patients were quite different clinically from the cyanotic patients described above. Although one was minimally cyanotic at rest (case 39), the other three were cyanotic only on exertion. The age of onset of cyanosis was recorded as 4, 5, 7, and 8 years, respectively. The patients were somewhat small for their ages and were characterized by exercise intolerance, which had developed concomitantly with the onset of cyanosis.

They were considered to be reasonable surgical risks and were therefore operated upon. One patient died in the immediate postoperative period. At autopsy, it was observed that the surgical patch was intact and that complete closure of the defect had been achieved. The pulmonary arterioles were noted to have severe medial thickening and intimal proliferation. After surgical correction, the three surviving patients were without cyanosis at rest or on exercise. Their exercise tolerance increased considerably, and at catheterization 1 year later, one patient (case 39) revealed a fall in the pulmonary arterial pressure from preoperative values of 90/50 mm. Hg, with a mean of 60, to postoperative values of 60/12 mm. Hg, with a mean of 24.

It is not possible to identify the particular

physiologic course followed by these patients to their state of high pulmonary vascular resistance and cyanosis. This point in the natural history could be reached either by failure of pulmonary vascular maturation or by normal pulmonary vascular maturation followed by progressive pulmonary vascular changes. Some patients do reach this stage of severe pulmonary change and poorer prognosis.

Postoperative Studies

Knowledge of the influence of surgical correction on the natural history of a ventricular septal defect is important both in understanding the functional pathology and in determining the optimal time of treatment. The initial result of a "curative" surgical procedure upon the course of the lesion as defined physiologically is seen in figure 14.

Despite the dissimilarity of the patients' stages at the time of surgical intervention, and despite the number of courses potentially leading to a particular stage, the response to surgical correction was uniform: in the majority, physiologic study approximately 1 year after surgical intervention revealed essentially no change in total pulmonary resistance. The pulmonary blood flow was reduced, in many instances drastically, to normal levels. The mean pulmonary arterial pressure was decreased sharply to normal or nearly normal values.

These findings would suggest that the pulmonary arterioles show little change in the direction of more normal structure, at least in the first postoperative year. The dramatic changes in pulmonary pressure and flow depend on the elimination of the left-to-right shunt present before surgical therapy. Knowledge of the late response of the pulmonary vascular bed to closure of the ventricular septal defect must await restudies years or even decades after corrective surgery.

Comment

This group of cases may not be representative of all isolated ventricular septal defects. Many factors influence the type of patient seen at a particular institution and hence serve to bias the selection. The factors resulting in multiple catheterization studies will tend to influence the selection still further; but these appear minimal here, since this group experience parallels the total experience in patients with isolated ventricular septal defect seen at our institution during the last 6 years.

It is important to recall that this communication deals with patients having only isolated ventricular septal defect. Additional anomalies may profoundly alter the physiologic situation and also the resultant natural history of the lesion.

In the hemodynamics of ventricular septal defect, the location of the defect has been deemed to be of some importance. Abbott[21] has proposed that a ventricular septal defect with a right-to-left shunt represents a specific entity arising out of the anatomic relationships between the ventricular septal defect and the aortic root. This hypothesis no longer seems tenable, for a large defect located anywhere in the membranous septums can be associated with a right-to-left shunt.[3, 22-24] In addition, certain defects in which the aorta overrides the right ventricle anatomically nevertheless shunt only left-to-right. Finally, in the defect characterized by origin of both great vessels from the right ventricle without pulmonary stenosis, either left-to-right or right-to-left shunting can occur.[25] Location of the defect in various portions of the membranous septum in the patients in this series had no apparent influence on the course followed. No conclusion may be drawn from the course followed by the one patient with a muscular septal defect.

The *size* of the ventricular septal defect did appear to be of major consequence. Those patients with openings of less than 1 cm. per M.^{2} of body surface area had minimally altered physiologic responses, were essentially without symptoms, and revealed no change during the period of observation.

Two specific influences of the large defect (greater than 1 cm. per M.^{2} of body surface area) are worthy of note. In some infants, a relative decrease in defect size resulted in a definite alteration in physiologic response. Moreover, the very large defect (larger than 4 cm. per M.^{2} of body surface area) influenced

the surgical mortality. Apart from these consequences, however, the precise size of the defect beyond 1 cm. per M.^{2} of body surface area did not critically influence the physiologic course followed by the patient.

The symptomatologic and physiologic status in a patient with a large ventricular septal defect is probably primarily influenced by the state of the pulmonary vascular bed. In the normal child during the first 4 years of life the pulmonary vasculature undergoes maturation from its fetal state to its normal adult condition.

In the presence of a large ventricular septal defect the following possibilities may occur: (1) the pulmonary vessels may develop normally (group IC), (2) maturation of the pulmonary vessels may be delayed (group II), or (3) maturation may fail to occur (group III). This concept of normal or altered pulmonary vascular maturation appears vital to an understanding of the natural history of ventricular septal defect.

A second phenomenon observed in patients with large defects was the series of changes indicative of progressive pulmonary vascular disease (group IV). The wide range in age of onset of these changes makes it difficult to predict the occurrence of progressive vascular disease in the individual patient.

An appreciation of the state of the pulmonary vascular bed is necessary in defining the stage of the disease process that a particular patient has reached. In our experience, knowledge of pressures in the pulmonary circuit has not provided this information. High pulmonary arterial pressures may be present in patients with normal pulmonary resistance. The high pressures may be maintained by greatly augmented pulmonary flow (hyperkinetic pulmonary hypertension), by high total pulmonary resistance (obstructive pulmonary hypertension), or by both.

As a prognostic sign, high pulmonary arterial pressure usually indicates a large defect but provides no information regarding the state of the lungs. Progressive pulmonary vascular disease does occur in the presence of a stable pulmonary arterial pressure. This is because in the case of a large ventricular septal defect free or nearly free communication exists between the two ventricles. If pulmonary resistance is less than systemic resistance, then the systemic resistance will determine the ventricular pressure necessary to maintain an adequate cardiac output. The lesser resistance in the pulmonary circuit necessitates the hyperkinetic effect of increased pulmonary blood flow (left-to-right shunt) to maintain the pressure in the ventricle at its obligatory level. As the pulmonary resistance approaches the level of systemic resistance, a lesser augmentation of pulmonary blood flow is required. If pulmonary resistance exceeds systemic resistance, then the pulmonary resistance determines the pressure in the ventricles necessary for an adequate cardiac output. Pressure in the pulmonary and systemic circuits will therefore rise as pulmonary obstructive disease progresses. Now the hyperkinetic effects are needed in the systemic circuit, and right-to-left shunting occurs. Until it exceeds the systemic resistance, however, a rising pulmonary resistance may not produce an increase in pulmonary arterial pressure.

On the other hand, an increasing pulmonary arterial pressure does not necessarily mean progressive pulmonary vascular disease. A normal increase in systemic resistance during childhood will necessitate a higher left ventricular pressure. In the presence of a large ventricular defect this increased pressure will be reflected in the pressure of the pulmonary artery. Pulmonary resistance may remain unchanged, and augmentation of pulmonary blood flow will result.

Thus a knowledge of pulmonary blood flow, as well as pressure, is essential in evaluating the patient with a ventricular septal defect. These two factors may be considered separately, or they may be combined as "resistance."

Measurements of total pulmonary resistance, while less accurate, have allowed assessment of the degree of pulmonary vascular maturation and an estimate of the progressive pulmonary obstructive lesions. The significance of a particular value of total pulmonary resistance depends to a large extent

on the age of the patient. For example, a value for total pulmonary resistance of 900 dynes second cm.$^{-5}$ at 6 months of age is within normal range. The same value in the same patient at 4 years of age is abnormal. Even a decrease in total pulmonary resistance from the normal 6-month level if less than that achieved by normal children suggests abnormality of the vascular bed.

The crucial point of this concept is that in measurements recorded during physiologic and histologic maturation, failure of the total pulmonary vascular resistance to increase does not necessarily mean that the pulmonary vascular bed has continued to be normal. Failure or delay in maturation of the pulmonary vascular bed may be as important as, and probably more common than, progressive pulmonary vascular disease, at least during childhood. Viewed in this light, the apparently irreconcilable differences of opinion expressed in the literature are understandable. Those who report no observed increase in pulmonary arterial pressure or in total pulmonary resistance in the childhood years are in the main correct. On the other hand, the clinical and histologic evidence that severe pulmonary vascular disease exists in some patients despite stable physiologic values is not negated. In addition to the infrequently seen rising total pulmonary resistance, failure or delay in the normal fall of the pulmonary resistance indicates that the pulmonary vascular bed is abnormal.

Surgical Consideration

The physiologic consequences of a large ventricular septal defect, and normal pulmonary vascular maturation are incapacitating and frequently critical during infancy. In our institution, infants with isolated ventricular septal defects and with congestive heart failure ensuing prior to 6 months of age, suffer a 25 per cent mortality in the first 2 years of life when treated medically. Ideally, prompt surgical intervention in these patients should be the goal.

In the patient with a large ventricular septal defect and with delayed or absent pulmonary vascular maturation, the earlier the surgical correction of the defect, the greater is the potential for reestablishing the normal maturational process. Although our contention is still subject to verification, we believe that early surgical intervention under these circumstances offers the most favorable prognosis. For whatever the initial response of the lung in a patient with a large ventricular septal defect, the potential for progressive pulmonary vascular disease always exists. Early surgical closure would prevent this serious complication.

The increased operative mortality among infants, however, does impose decided limits on surgical therapy. In our experience, this becomes minimal after age two. Moreover, if the defect is to decrease in size, it will have done so by that time. Other factors being equal, we believe 2 years of age or older to be the optimal time for surgical correction of a large ventricular septal defect. We make this recommendation on the basis of a currently low rate of surgical mortality (less than 5 per cent). A comparable mortality rate has been achieved at a number of other centers under the same circumstances.

For the severely ill infant under 2 years, selecting the wisest form of therapy is a vexing problem. While the mortality rate with medical therapy is considerable, surgical treatment has also resulted in high mortality rates. Our current practice has been to defer operations on these infants, if possible, and to extend surgical treatment only to those who appear unlikely to survive. Another approach to the patient in this category has been a two-stage procedure, banding of the pulmonary artery followed by closure of the defect at a later time. Clarification of the relative merits of medical treatment and the one-stage and two-stage surgical technics will be achieved only through experience. The results of the application of each of these therapeutic methods leave a great deal to be desired. Substantial reduction in the mortality in this age group achieved through any of the above methods would, of course, alter our present therapeutic procedures.

The advisability of surgical intervention at the two extremes of the spectrum of disease remains at issue. Patients with small defects

undergo little or no physiologic change in the pediatric years. While the risk of subacute bacterial endocarditis and the possibility of pulmonary vascular disease in later years must be considered, the need for surgical intervention does not appear urgent. Under this circumstance, one should have a critical knowledge of the surgical mortality rate observed at the center proposing treatment. If it is truly minimal (i.e., less than 1 per cent for this good-risk category) then these patients would benefit from elective surgical correction of their defect.

No agreement has been reached about the appropriate therapy for the older child with high pulmonary resistance (severe pulmonary vascular disease). In those patients with right-to-left shunts and without any left-to-right shunting, no short-term benefits accrue from surgical correction that would justify the surgical mortality encountered. It is not known whether regression of the pulmonary vascular changes ultimately does or does not occur after closure of the defect.

Patients with residual left-to-right shunts as well as the right-to-left flow appear to benefit immediately from defect closure in proportion to the magnitude of the left-to-right flow. We therefore customarily advise surgical correction in these patients.

Conclusion

The natural history of the isolated ventricular septal defect is variable and as yet incompletely defined. In the varying responses of the pulmonary vascular bed to presumably identical stresses lies the key to further knowledge of this affliction. Advances in the understanding of pulmonary hypertension, similar to those advances made in the knowledge of systemic hypertension, are clearly required. Presently one can only recognize the several possible courses open to the patient with a large ventricular septal defect. This variability of response is in itself of major importance. It should alert the clinician and surgeon alike to the need for careful and precise evaluation of each patient presenting with a ventricular septal defect. Even more important, the very existence of several different adaptations to a presumably identical stress should serve as a warning against making any single generalization about the natural history and therapy of this disorder at the present time.

Summary

Forty patients with isolated ventricular septal defect were studied physiologically two or more times before they underwent surgical treatment. Utilizing baselines obtained by heart catheterizations of normal infants and children, we grouped patients with ventricular septal defect according to the magnitude of the total pulmonary resistance, pulmonary blood flow, and pulmonary arterial pressure, and according to changes in these values over time. The patients with small defects (less than 1 cm. per M.^{2} of body surface area) were easily separable on the basis of physiologic findings. Patients with large ventricular septal defects (greater than 1 cm. per M.^{2} of body surface area) exhibited one of three possible initial responses to the stress of high pulsatile pulmonary flow and increased pulmonary artery pressure: (1) normal regression of total pulmonary resistance; (2) delayed fall in total pulmonary resistance; (3) failure of the total pulmonary resistance to decrease with age.

These physiologic responses were thought to be related to normal maturation, delayed maturation, or failure of maturation of the pulmonary vascular bed. It was observed that a subsequent increase in total pulmonary resistance could be superimposed on any of the three initial responses at any time. Clinical evidence and catheterization data suggested that the relative size of the ventricular septal defect had decreased in five patients.

The variability of the physiologic courses, the importance of the pulmonary vascular bed in determining these responses, and our lack of understanding of the etiology of the pulmonary vascular changes were noted.

The indications for, and timing of surgical intervention in patients with isolated ventricular septal defects, are discussed in light of the above findings.

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Isolated Right Ventricular Hypoplasia with Atrial Septal Defect or Patent Foramen Ovale

By MARVIN A. SACKNER, M.D., MORTON J. ROBINSON, M.D., WILLIAM L. JAMISON, M.D., AND DAVID H. LEWIS, M.D.

IN 1936, Taussig[1] stated that a diminutive right ventricle is always associated with underdevelopment or malformation of the tricuspid or pulmonic valves. Four cases of hypoplastic right ventricle unassociated with valvular defects have been reported in recent years. A patent foramen ovale or atrial septal defect has been an accompanying anomaly. All cases have been described in cyanotic infants or young children. In 1950, Cooley and his associates[2] made the diagnosis by angiocardiography and confirmed it at necropsy. In 1959, Gasul and co-workers[3] established the diagnosis in a 4-year-old child at thoracotomy. In 1961, Medd and associates[4] defined the pathologic features in two siblings who died during infancy.

We have observed three adults with this disorder who were members of the same family. The purpose of this paper is to describe the clinical and hemodynamic features that are sufficiently characteristic to enable a definitive diagnosis. In addition, a fourth case obtained from the postmortem files of the Philadelphia General Hospital is briefly reported for historic interest.

Case Report

A 2-month-old white boy was admitted to the Philadelphia General Hospital in September 1935 because of fever and dyspnea of 1 week's duration.

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Physical examination revealed an acutely ill cyanotic infant in respiratory distress. The pulse was 160, the respirations 70, and the temperature 105 F. The weight was 4.6 Kg., the height 55 cm. Erysipelas was present on the face and scalp. Both ear drums were perforated and discharging pus. Rhonchi were heard in both lung fields. The heart was of normal size by percussion. The rhythm was regular, and no murmurs were heard. The hemoglobin was 12 Gm. per 100 ml. and the white cell count 4,800. There was 2+ proteinuria. The patient was treated with immunotransfusions but died 6 days after admission.

The clinical diagnoses were bilateral otitis media, erysipelas, and bronchopneumonia. The necropsy diagnoses were isolated hypoplasia of the right ventricle, erysipelas, and bronchopneumonia.

The aorta, venae cavae, and pulmonary veins were normal. The ductus arteriosus was closed. The pulmonary artery was underdeveloped.

The heart weighed 20 Gm. (fig. 1). The right ventricular chamber was small; its lowermost portion reached less than one half the distance from the base to the true cardiac apex. The distance from the base of the tricuspid valve to the lowermost portion of the right ventricle was 1.2 cm. The distance from the base of the mitral valve to the lowermost portion of the left ventricle was 2.9 cm. The tricuspid valve was small, but of normal shape and insertion. The right atrium was dilated. The left ventricle showed hypertrophy. The foramen ovale was probe-patent.

Cases in Family E

The family pedigree is depicted in figure 2. Unfortunately, the unwillingness of many family members to be examined prevented full-scale genetic investigation. As far as can be determined, no consanguinity existed nor were there any abnormal pregnancies.

Case II-1

F.E., a 30-year-old Negro laborer was in good health until May 1953, when he fainted after a hot day's work in a coal mine. A company physician found a blood pressure of 120/95 and a pulse of 80. The cardiac impulse was diffuse with maximum intensity in the fourth interspace at the

anterior axillary line. The rhythm was regular but frequent extrasystoles were present. There were blowing aortic and apical systolic murmurs. The hemoglobin was 18 Gm. per 100 ml., and the white cell count was normal. The urine showed 3+ proteinuria. The chest roentgenogram and electrocardiogram were consistent with left ventricular enlargement. A diagnosis of aortic stenosis was made and the patient was not allowed to return to work.

Subsequently, despite moderately strenuous work as a porter, he remained asymptomatic until November 1958. At this time, he noted the gradual onset of leg swelling. He was admitted to the Philadelphia General Hospital in December 1958. He denied dyspnea, orthopnea, hemoptysis, and chest pain. He had no complaints referable to the gastrointestinal or genitourinary systems. He denied rheumatic fever and syphilis.

On physical examination, except for marked pitting edema extending up to the level of the eleventh thoracic vertebra, he did not appear ill and had no orthopnea. The blood pressure was 110/80, the pulse 80, respirations 22, and temperature 98 F. The weight was 89 Kg., the height 200 cm., the arm span 206 cm., and the upper segment-to-lower segment ratio 0.89 (normal, 0.93; Marfan's gene, 0.85.[5]) The fingers were long and tapered. The nailbeds, lips, and mucous membranes were moderately cyanotic. The cervical veins were distended at 90° and filled from below. The lungs were clear. The heart was greatly enlarged to the left, the point of maximum impulse was at the sixth interspace in the anterior axillary line. The rhythm was regular, with a few extrasystoles. There were a presystolic gallop over the entire precordium, a soft nonradiating ejection murmur at the aortic area, and a systolic click over the remaining precordium. The liver was tender and palpable 5 cm. below the costal margin. Peripheral pulses were normal.

The patient was treated with hydrochlorothiazide, digoxin, and procaine amide and became edema free after 3 weeks. He had lost 24 Kg. of edema fluid. Following this diuresis, cardiac catheterizations were performed (table 1).

Throughout the hospital course, the hemoglobin ranged from 17 to 18 Gm. per 100 ml. The white cell count and differential were normal. Total serum protein was 4.8 Gm. on admission but rose to 6.2 Gm. per 100 ml. after diuresis. Paper electrophoresis showed an albumin of 2.7 Gm. and globulin of 3.5 Gm. with normal fractions. There was a persistent proteinuria ranging from 1.0 to 3.5 Gm. daily.

The electrocardiogram showed prolonged P-R interval, occasional premature ventricular contractions, biatrial enlargement, and left ventricular

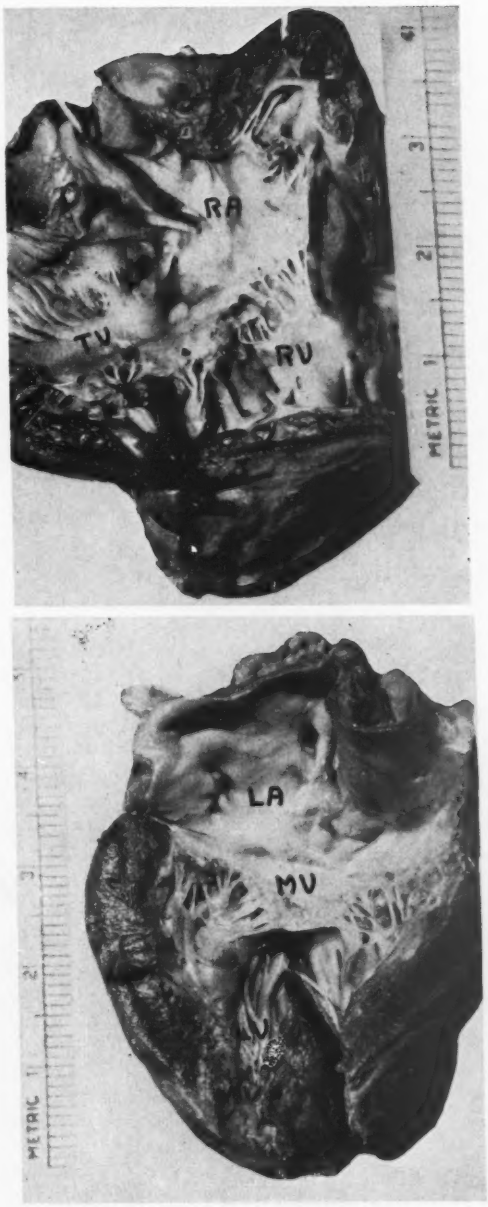

Figure 1

The dissected heart of case J.E. The right ventricular chamber is diminutive yet the myocardium is of normal thickness; the left ventricle is moderately hypertrophied (RA, right atrium; TV, tricuspid valve; RV, right ventricle; LA, left atrium; MV, mitral valve; LV, left ventricle).

Table 1

Hemodynamic Data

Case	Age, years	Date	Pressures (mm. Hg)						Oxygen content (vol. %)*						Arterial oxygen saturation (%)
			RA	RV	PA	PCA	LA	BA	IVC	SVC	RA	RV	PA	PV	LA	BA	
II-1	38	12/24/58	(12)	36/13	30/14	(12)	—	114/72 (82)	—	10.29	13.88	15.54	14.77	—	—	16.31	70.0
	38	1/7/59	(11)	—	23/12	(16)	(11)	(11)	108/60 (72)	17.08	10.88	15.68	16.79	18.42	23.66	22.10	21.76	90.0
II-4	22	9/18/56	(7)	25/11	22/13	(15)	(7)	—	140/80 (105)	—	—	21.34	20.55	20.14	—	—	26.98	84.5
III-1	6	1/21/54	(3)	20/2	23/10	(14)	—	—	—	10.20	10.57	13.25	12.30	—	—	13.80	78.0
	12	3/28/60	(9)	33/10	30/11	(13)	(9)	—	—	10.02	14.19	15.58	15.69	—	—	—	—

*Mean of multiple samples.

Abbreviations: RA, right atrium; RV, right ventricle; PA, pulmonary artery; PCV, pulmonary capillary venous; LA, left atrium; BA, brachial artery; IVC, inferior vena cava; SVC, superior vena cava; PV, pulmonary vein.

hypertrophy. The mean QRS axis was −50° (fig. 3). The chest roentgenogram showed an enlarged, globular heart and increased vascular markings with a normal pulmonary conus (fig. 4).

The patient refused surgery and was discharged to the outpatient clinic after 8 weeks of hospitalization. He returned to work and did well except for transient peripheral edema that responded to mercurial injections. He denied dyspnea and orthopnea, and his lung fields remained clear of rales.

In March 1960, intractable ascites and peripheral edema developed. Also, he noted weakness, myalgia, and blurred vision. He was readmitted to the hospital with the diagnoses of digitalis toxicity and hypopotassemia.

Physical examination was little changed from the previous admission except for slow atrial fibrillation (40 per minute), left pleural effusion, ascites, and more intense cyanosis.

The blood urea nitrogen was 119 mg., the serum creatinine 3.8 Gm., and the uric acid greater than 10 mg. per 100 ml. Serum potassium was 2.5 mEq. per liter.

The electrocardiogram showed atrial fibrillation, multifocal premature ventricular contractions, and short runs of ventricular tachycardia. The withdrawal of digitalis and intravenous administration of potassium chloride improved the arrhythmia. Despite thoracentesis and vigorous attempts at diuresis, the patient remained in severe right-sided congestive heart failure. Three weeks after admission, he complained of a suffocating feeling and became noticeably dyspneic for the first time. He was found dead in bed the next day.

The clinical diagnosis was atrial septal defect and idiopathic enlargement of the left ventricle. The necropsy diagnoses were isolated hypoplasia of the right ventricle, atrial septal defect, mild aortic stenosis due to fibrosis and calcification, left ventricular hypertrophy, left ventricular endocardial fibroelastosis, congestive heart failure, and bronchopneumonia.

The aorta, venae cavae, pulmonary veins, and coronary vessels were normal. The pulmonary artery was slightly narrowed.

The heart weighed 650 Gm. (fig. 5). The right ventricle was small, its lowermost portion reached less than one half the distance from the base to the true cardiac apex. The chamber proportions are depicted schematically in figure 6. The tricuspid valve was normal in shape and position; there was functional dilatation of the ring. The aortic valve was distorted by fusion of all the commissures, fibrous thickening of the free and closing margins of the cusps, and irregular calcified nodules between the cusps; the valve area was 1.9 cm.^{2} The endocardial surface of the left ventricular wall was dull gray, and histologic examination

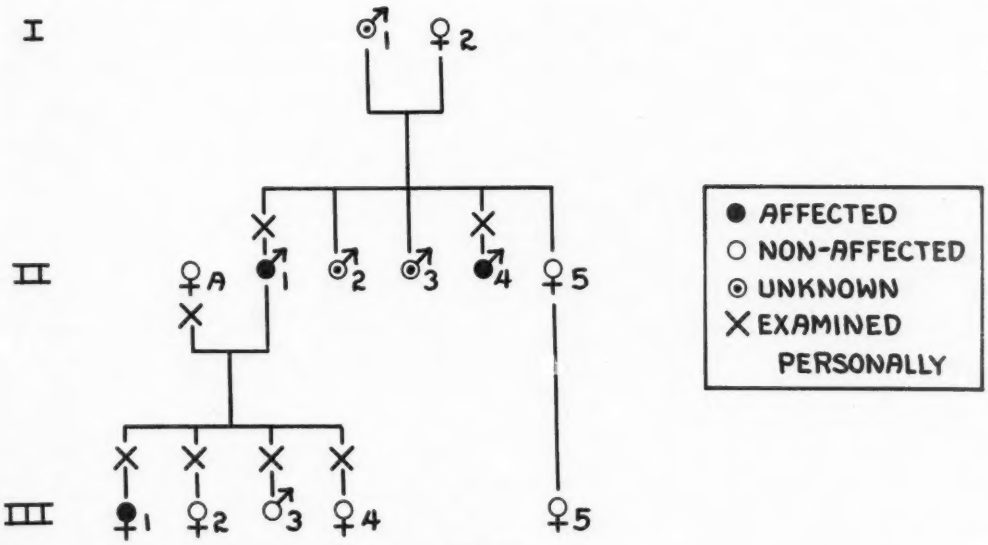

Figure 2

Pedigree of family E: I-1, T.E., age 60 years, worked all his life as a coal miner, never hospitalized; I-2, M.E., died at age 56 years, cause of death was uremia, had diabetes mellitus; II-1, propositus, F.E., died at age 39 years, right ventricular hypoplasia; II-2, G.E., age 35 years, employed as coal miner, served in Army; II-3, S.E., age 31 years, employed as coal miner, served in Army; II-4, C.E., died at age 22 years, right ventricular hypoplasia; II-5, E.E., age 23 years, good health; III-1, Ca.E., age 13 years, right ventricular hypoplasia; III-2, H.E., age 11 years, good health; III-3, age 5 years, good health; III-4, age 3 years, good health; III-5, age 1 year, good health.

showed proliferation of fibroelastic tissue. The right ventricular endocardium was normal. The left ventricular wall measured up to 19 mm. in width; the right, 4 mm. Glycogen, amyloid, trichrome, mucopolysaccharide, fat, and elastic tissue stains of the myocardium were unremarkable.

Both atria were markedly dilated as were the atrial appendages, which were filled with adherent, partially organized thrombus. There was an oval, smooth-walled atrial septal defect, which measured 4.5 cm. in diameter.

All viscera showed marked passive congestion.

Case II-4

C.E., was a 22-year-old janitor who had cyanosis and easy fatigability dating from childhood. Nevertheless, he enjoyed fair health and always held a job. In July 1956, on a routine physical examination, a hemoglobin of 22 Gm. per 100 ml. was discovered. He was treated with monthly phlebotomies and was referred to the Charleston General Hospital in September 1956.

Physical examination revealed a cyanotic but otherwise healthy appearing man. The blood pressure was 130/100 and the pulse 96. The weight was 76 Kg., the height was 185 cm. The fingers were long and tapered; clubbing was present. The lungs were clear. The heart was enlarged to the left. The rhythm was regular. There were a moderately loud, holosystolic murmur in the third interspace parasternally, a short basilar diastolic murmur, and an apical presystolic murmur or gallop. The liver was nontender and palpable just below the costal margin. There was no peripheral edema.

The hemoglobin was 22 Gm. per 100 ml., the hematocrit level 73 per cent, and the white cell count 7,000. The blood urea nitrogen was 17 mg. per 100 ml. There was persistent proteinuria, ranging from 1+ to 3+.

The electrocardiogram showed right atrial enlargement and left ventricular hypertrophy. The mean QRS axis was –45° (fig. 3). The chest roentgenogram showed moderate cardiac enlargement and a slight decrease in vascular markings (fig. 7). Cardiac catheterization (table 1) and venous angiocardiography (fig. 8) were carried out. The diagnosis of an atypical tricuspid atresia was made and the patient was discharged to await surgery.

In August 1957, the patient underwent thoracotomy. The right ventricle and pulmonary artery

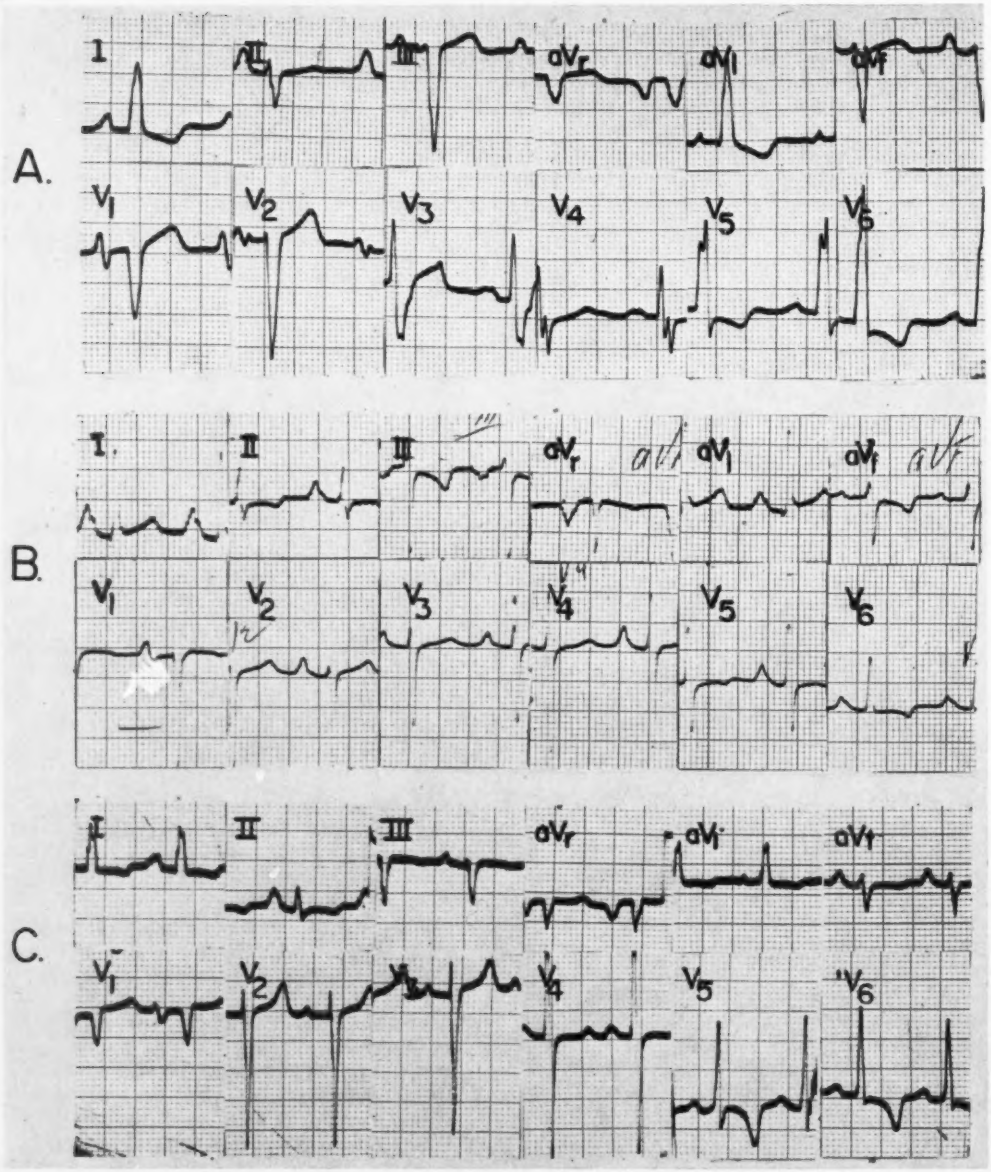

Figure 3

Electrocardiograms of Family E: A-II-1, B-II-4 (the precordial leads are one-half standard), and C-III-1. There is a remarkable similarity: all show left axis deviation, atrial enlargement, left ventricular hypertrophy with "strain" pattern, and top normal or prolonged P-R interval.

were markedly underdeveloped, the atria and left ventricle were enlarged. The tricuspid and pulmonic valves were hypoplastic but not atretic, insufficient, or stenotic. A fenestrated atrial septal defect about 3 cm. in diameter was present. No corrective procedure was attempted. Postopera-

tively, the patient did poorly. He had frequent episodes of pleuritis and bronchitis. He died at home in congestive heart failure in 3 months. No necropsy was obtained.

Case III-1

Ca.E.* is a 13-year-old schoolgirl. At the age of 5 years, during examination for a foreign body in the auditory canal, a harsh holosystolic murmur was heard parasternally. Except for frequent attacks of tonsillitis and pharyngitis, the patient had been asymptomatic. No cyanosis, clubbing, or hepatomegaly was noted. The hemoglobin was 14 Gm. per 100 ml. The electrocardiogram and chest roentgenogram were suggestive of early left ventricular enlargement. The lung fields showed a slight increase in vascular markings. Cardiac catheterization (table 1) was performed, and a diagnosis of ventricular septal defect was made.

After a tonsillectomy at age 8 years, she had no further attacks of frequent respiratory infections. Her lips became blue on occasion and she had been on a program of limited physical activity. In September 1959, she began to participate in school gymnastics and noted easy fatigue compared to her classmates. In January 1960, she had a cold that was followed by ankle edema and moderate dyspnea, but no orthopnea. The patient was then admitted to the Hospital of the University of Pennsylvania.

Physical examination revealed an acutely ill girl who lay flat in bed with minimal discomfort. She was cyanotic and had moderate pretibial and pedal edema. The blood pressure was 125/70, the pulse 90. The cervical veins were distended at 90°, and filled from below. There were fine rales and rhonchi in both lung fields. The heart was enlarged to the left. The rhythm was regular. There was a loud holosystolic, harsh murmur parasternally, which radiated to the apex. A protodiastolic gallop was present. The liver was palpable 5 cm. below the costal margin and was nontender.

The patient was treated with bed rest, diuretic agents, and digitalis. During the first 72 hours she lost 5 Kg. and during her hospitalization 9 Kg. of edema. After the diuresis, the gallop rhythm disappeared though the systolic murmur persisted.

The hemoglobin ranged from 13.5 to 15.9 Gm. per 100 ml. and there was persistent 2+ proteinuria. The total serum protein was 6.4 Gm.; albumin 3.0 and globulin 3.4 Gm. per 100 ml. The electrocardiogram showed right and left atrial enlargement and left ventricular hypertrophy. The mean QRS axis was −30° (fig. 3). The chest roentgenogram showed nonspecific cardiac enlargement and a slight decrease in pulmonary vascularity (fig. 9). Cardiac catheterization (table 1) and venous angiocardiography (fig. 10) were performed.

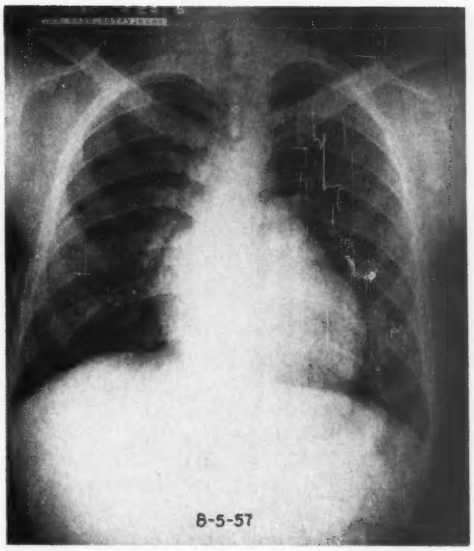

Figure 4

Chest roentgenogram of case II-1.

The patient is permitted limited activity and is fairly well compensated except for paroxysmal supraventricular and ventricular tachycardia.

Cardiac Catheterization

These data are summarized in table 1 and figure 11. None of the cases showed clinical evidence of congestive heart failure at the time of their study; cases II-1 and III-1 had been digitalized. The pulmonary arterial pressures were normal. There was significant elevation in right ventricular end-diastolic pressures (except in the first catheterization in case III-1). No pressure gradient was found across the pulmonic or tricuspid valve. Right atrial pressure equaled left atrial or pulmonary capillary venous pressure in individual cases. A step-up in oxygen content at the atrial level was consistent with atrial septal defect in cases II-1 and III-1; the data in case II-4 were incomplete. Higher concentrations of oxygen in the right ventricle or pulmonary artery were compatible with incomplete mixing of the shunted blood when

*Details of this case were furnished through the courtesy of Dr. John H. Helwig, Jr., Associate in Medicine, University of Pennsylvania School of Medicine.

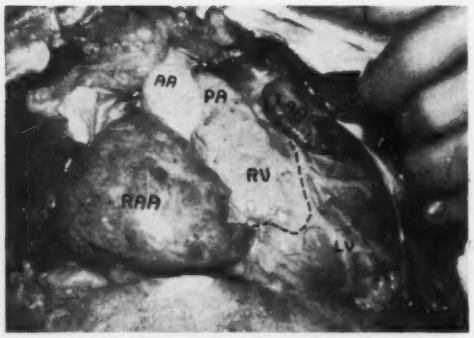

Figure 5A

Heart of case II-1. Heart is shown in situ; the hypoplastic right ventricle is readily apparent. RAA, right atrial appendage; RV, right ventricle; LV, left ventricle; LAA, left atrial appendage; PA, pulmonary artery; AA, ascending aorta.

other data were taken into account. For example, in case II-1, the data also suggested ventricular septal defect. This was excluded by the failure to record the characteristic murmur in the right ventricle at the time of cardiac catheterization.[6] Although the findings in case III-1 were consistent with ventricular septal defect at the time of the first catheterization, the data indicated atrial septal defect at the second catheterization. Nevertheless, it appears from a further step-up in oxygen content that a ventricular septal defect is present as well. Oxygen samples low in the atrium and near the valve were not significantly different from the ventricular samples. Finally, all patients showed arterial oxygen desaturation from right-to-left shunting through the atrial septal defect.

Angiocardiography

These were difficult to interpret in the anteroposterior projection (figs. 8 and 10) and reference should be made to the pathologic specimen (fig. 5) for orientation. The right atrium was dilated and there was early appearance of dye in the left atrium signifying right-to-left shunt. Because of superimposition of the right ventricle on the left atrium, the full extent of the right ventricle was difficult to distinguish with certainty.

Figure 5B

Same case as figure 5A. Shows diminutive right ventricle whose size is the same as the atrial septal defect. The close proximity of the atrial septal defect to the inferior vena cava probably accounts for the high oxygen content in the latter vessel obtained at cardiac catheterization. ASD, atrial septal defect; RA, right atrium; TV, tricuspid valve; IVC, inferior vena cava.

Nevertheless, it appeared small in contrast to the dilated hypertrophied left ventricle. The pulmonary artery was small but not disproportionate to the right ventricle.

Discussion

Anatomy

The defect was characterized by a small right ventricular chamber with normally separated and positioned tricuspid and pulmonic valve leaflets. The tricuspid valvular ring was small or functionally dilated by heart failure. The myocardium was thin or of normal thickness and showed normal histologic features. Its vascular supply was normal. The atria were dilated and hypertrophied because of the

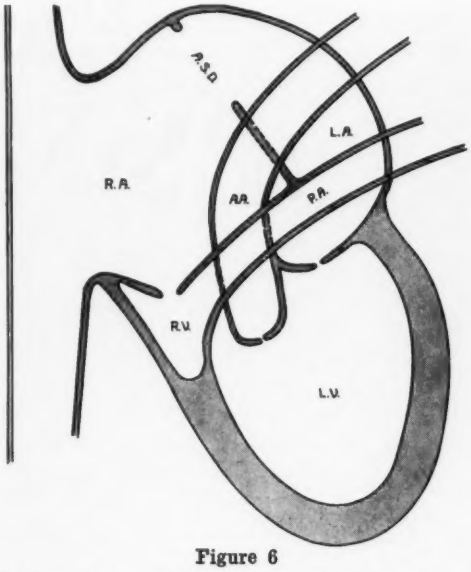

Figure 6

Schematic view of heart of case II-1. The relative dimensions obtained at necropsy are depicted (for abbreviations see figure 5A and B).

Figure 7

Chest roentgenogram of case II-4.

interatrial shunt and the restriction to filling offered by the hypoplastic right ventricle. In the 2-month-old baby in the present paper and the two infants reported by Medd et al.,[4] the foramen ovale was patent but competent. In the older patients, the 4-year-old child reported by Gasul et al.[3] and cases II-1 and II-4, 39 and 22 years old, respectively, an atrial septal defect was present. The left ventricle was dilated and hypertrophied presumably because it bore the brunt of the circulation. In case II-1, a mild aortic stenosis and left ventricular fibroelastosis were found but were not considered to play a significant part in the clinical picture.

This disorder must be differentiated from right ventricular hypoplasia associated with other malformations. By far, the most common of these is tricuspid atresia. Pulmonary atresia with closed ventricular septum, overriding of the tricuspid valve as in some cases of complete transposition of the great vessels, and tricuspid stenosis may also be responsible. In Ebstein's malformation, the right ventricle is of thin or normal thickness but its cavity is always diminished by a downward displacement of the tricuspid valve. Cooley et al.[2] mentioned a case of right ventricular hypoplasia secondary to an absence of the right coronary artery. Finally, Uhl[7] reported a 7-month-old child in whom the right ventricular myocardium was replaced by fibrous tissue ("parchment heart"). In this anomaly the right ventricular endocardium and epicardium were contiguous while the left heart and coronary vessels were normal. In contrast to the diminutive chamber in isolated right ventricular hypoplasia, the right ventricular chamber was dilated and filled with a large laminated thrombus.

Etiology

The etiology of this anomaly is unknown. Medd et al.[4] pointed out that the hypoplasia of the right ventricle may be a primary developmental anomaly or be secondary to a reduction of tricuspid flow during fetal life. It is of interest that five of the eight reported cases are familial. Moreover, it is the only type of congenital heart disease in the affected fami-

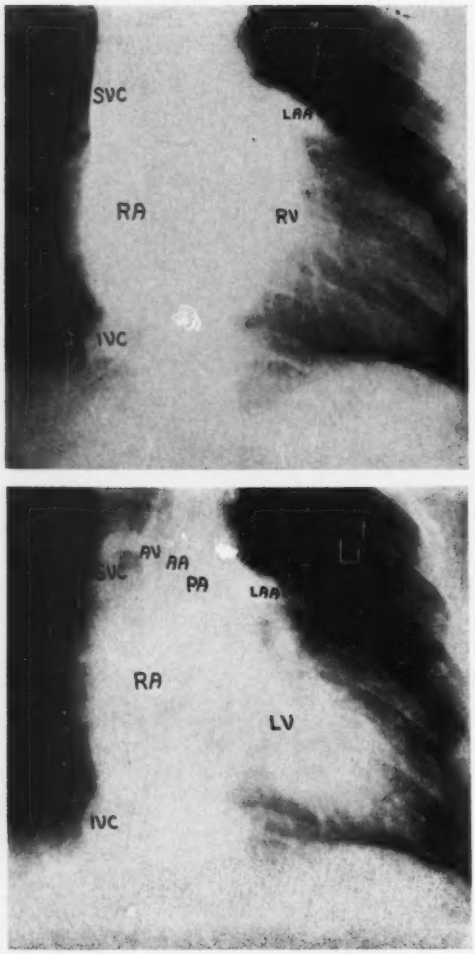

Figure 8

Angiocardiogram of case II-4. Films at 3 seconds (top) *and 5 seconds* (bottom) *after injection of radiopaque dye. Early opacification of the left side of the heart is seen, and the right ventricle appears diminutive. Radiopaque material refluxes into the inferior vena cava and azygos vein, indicating increased resistance to filling of the right ventricle or tricuspid regurgitation. The left ventricle is hypertrophied (for abbreviations see figure 5A and B; in addition, SVC, superior vena cava; AV, azygos vein).*

lies. This is in agreement with the observations of Wood,[8] who stated that congenital heart disease occurring in more than one member of a family is nearly always of the same type.

Hemodynamics

The case of Gasul et al.[3] and the three cases in the present report constitute the basis for this discussion; all had atrial septal defects. No data are available for those cases with patent foramen ovale who died during infancy.

The basic hemodynamic disturbance is the obstruction to inflow of blood into the right ventricle due to the small size of the chamber. Before puberty, the right ventricle end-diastolic pressure may be normal (Gasul et al.[3] and case III-1). There is a left-to-right atrial shunt but, in addition, a right-to-left shunt is present because the diminutive right ventricle cannot accept both the systemic return and the blood shunted from the left atrium. At this stage, the only manifestation of the restriction to inflow is a prominent "a" wave in the atrial pulse and on the right ventricular pressure tracing. With time, the small right ventricle dilates and the end-diastolic pressure rises but this still is inadequate. The mixed atrial shunt persists and the arterial desaturation provokes secondary polycythemia. Thus, the picture in the adult is that of a mixed atrial shunt, an elevated end-diastolic pressure in the right ventricle with a prominent "a" wave, and the absence of pulmonary hypertension, tricuspid stenosis, or pulmonary stenosis.

This is a unique situation previously described only in certain cases of Ebstein's malformation.[9] The recording of intracardiac pressure and intracardiac electrical potential simultaneously serves to differentiate this anomaly from isolated right ventricular hypoplasia. In Ebstein's malformation, right ventricular electrical potential is recorded with right atrial pressure pulse.[10] This denotes that the right ventricle forms part of the right atrial cavity.

Though the end-diastolic right ventricular pressure is approximately one third the systolic, a situation akin to chronic constrictive pericarditis, the pressure pulse contour is not the same. The striking feature in constrictive

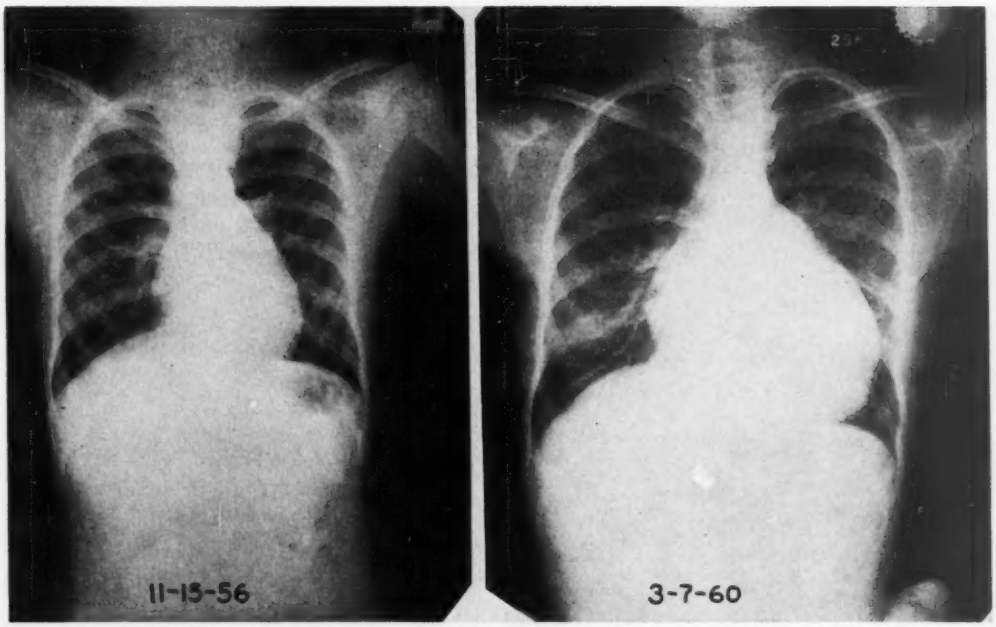

Figure 9

Chest roentgenograms of case III-1. At the age of 10 years, the heart is top normal in size and the pulmonary vascular markings are slightly increased. Three years later on March 7, 1960, the heart has undergone considerable enlargement and the pulmonary vascular markings are less prominent.

pericarditis is an early diastolic dip followed by a rapid rise of the diastolic pressure to form a plateau.[11] In contrast to the prominent "a" waves in the right atrial and ventricular pulse pressures in isolated right ventricular hypoplasia, giant "a" waves have not been noted.[12] Furthermore, arterial oxygen desaturation has not been observed in cases of atrial septal defect complicated by constrictive pericarditis.[13]

In case II-1, aortic stenosis had reduced the valve area to 1.9 cm.^{2}. Unfortunately, left heart catheterization was not carried out but on the basis of a theoretical formula relating pressure, flow and valve area,[14] it appears that the lesion was not hemodynamically significant.

Clinical Features

Habitus. If this anomaly is symptomatic at birth or an early age, development may be retarded. On the other hand, if symptoms develop after puberty, as in Family E, the patients are tall and slender, with normal or slightly decreased weight. The physiognomy is not consistent with that of the Marfan syndrome.

Cyanosis. This appeared at birth or in childhood and was a feature common to all the cases. Secondary polycythemia was present in the adults. Clubbing of the fingers was noted in two of the eight cases (Gasul et al.[3] and case II-4).

Dyspnea. In general, this was not a major complaint and was brought out usually with exercise. Nevertheless, the adults with the disorder were able to carry out moderately strenuous activity without discomfort (case II-1 was a coal miner).

Signs of Venous Congestion. All the adults showed elevated cervical venous pressure with prominent "a" waves, hepatomegaly, proteinuria, and peripheral edema at some stage

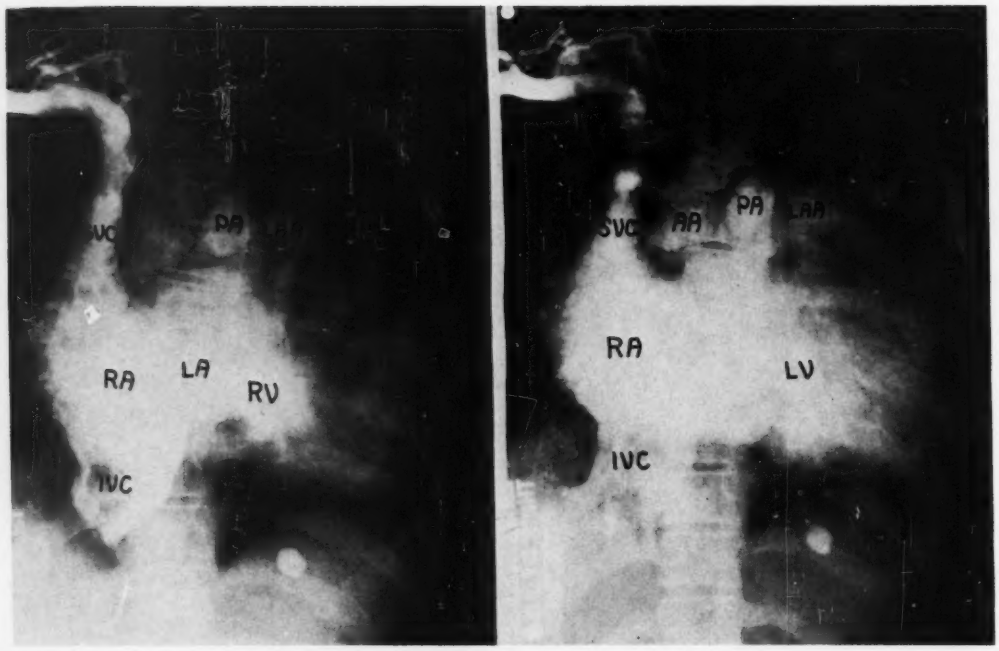

Figure 10

Angiocardiogram of case III-1. There is a 2-second interval between these films. Early opacification of the left side of the heart is seen and it appears that the right ventricle is diminutive. Radiopaque material refluxes into the inferior vena cava. The left ventricle is dilated.

of their disease. The elevated cervical venous pressure persisted even after diuresis to a dry weight. However, in Gasul's[3] 4-year-old child, after clearing of the presenting signs of ascites, edema, and increased cervical venous pressure, the right atrial pressure became normal. Finally, the two infants who died during the first week of life, both had pulsating livers.[4]

Signs of Pulmonary Congestion. Orthopnea was not recorded in any of the cases. Moreover, fine basilar rales were heard infrequently even in patients with marked right-sided failure.

Cardiac Impulse. The impulse was displaced to the left and was forceful though diffuse. In case II-1, an apex cardiogram revealed that the presystolic outward thrust was as prominent as the ventricular systole. This probably was due to the large amount of blood filling the left ventricle from a left atrium distended by the right-to-left shunt.

Cardiac Auscultation. There are no specific murmurs in this disorder though gallop rhythms are common. Thus, a presystolic gallop was heard in case 2 of Medd et al.,[4] in Gasul et al.,[3] and cases II-1 and II-4; a protodiastolic gallop was heard in III-1. The two infants and the baby in the present report had no murmurs. In cases II-4 and III-1, rather harsh pansystolic murmurs were heard parasternally. Their significance is questionable; perhaps they were due to a functional tricuspid insufficiency, though the contour of the pressure pulses from the right atrium did not lend support to this hypothesis. A regurgitant jet probably would not produce a large "v" wave, for the right atrial dilatation was extreme, and there was free communication with the left atrium. In case II-1 an attempt

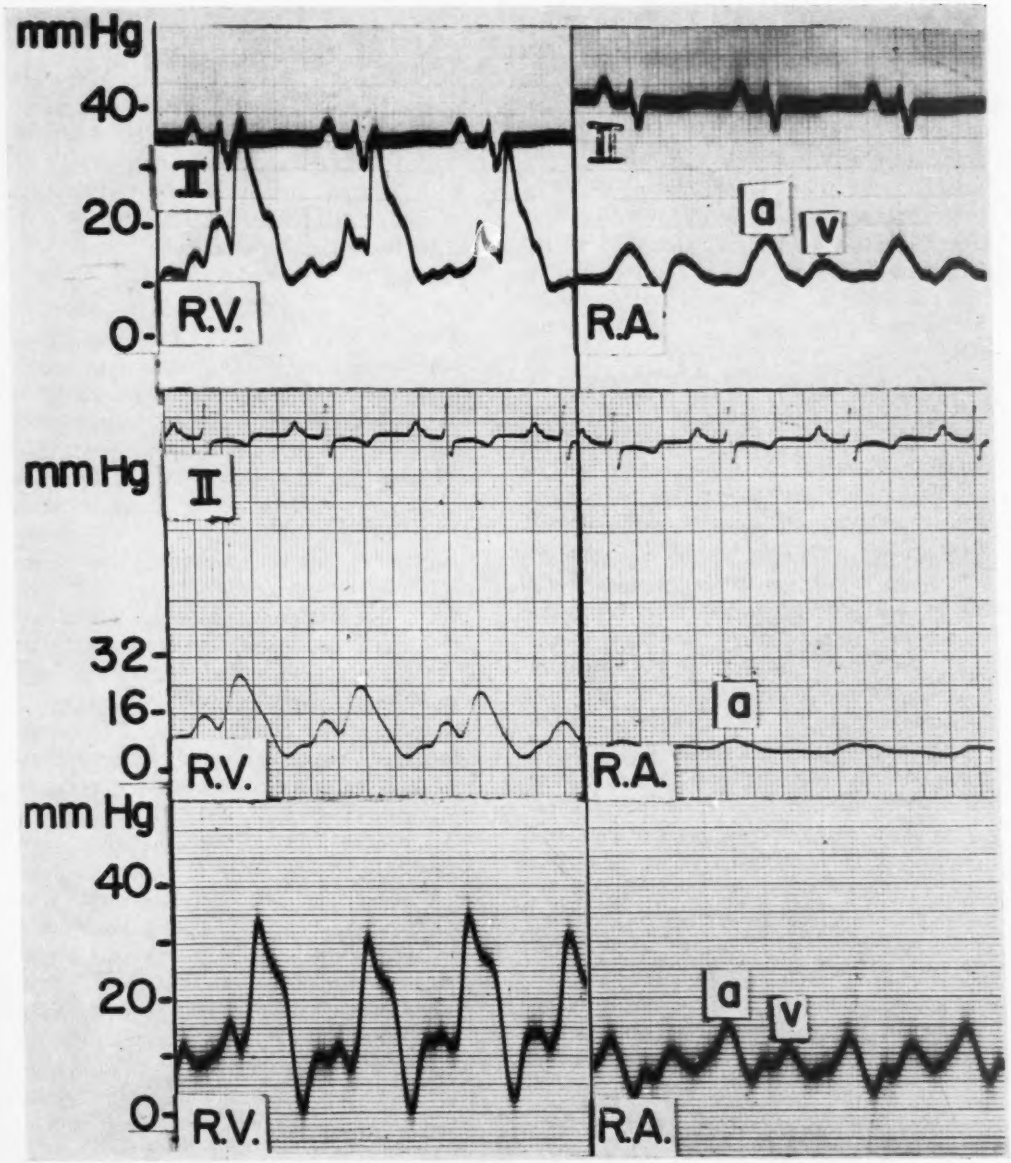

Figure 11

Pressure pulse tracings of the right ventricle (RV) and the right atrium (RA). From the top downward are cases II-1, II-4, and III-1. The curves are remarkably similar in contour (the tracings are damped in II-4). The right ventricular systolic pressures are normal or slightly increased; the end-diastolic pressures are increased. The "a" waves are prominent and superimposed on the ventricular pressure tracings.

was made to localize the source of the auscultatory findings by recording the intracardiac sounds. The presystolic gallop, which was transmitted widely over the precordium, originated wholly or in part from the right side of the heart (the left atrium and ventricle were not examined). The soft, blowing, ejection murmur at the aortic region originated in the pulmonary artery and was probably due to increased flow from the left-to-right interatrial shunt. Finally, the systolic click was not heard in the right side of the heart nor ascending aorta, and its site of origin is unknown.

Electrocardiography

The electrocardiographic features of isolated right ventricular hypoplasia are quite similar to those found in tricuspid atresia. In six cases of right ventricular hypoplasia (Gasul et al.,[3] Medd et al.,[4] Family E), all showed signs of left ventricular hypertrophy or absence of right ventricular potential in the precordial leads. There was left axis deviation in five cases, right axis in one case. Combined atrial hypertrophy was found in four cases, right atrial hypertrophy was found in two cases. In tricuspid atresia, a condition also associated with defective right ventricular development, practically all cases show left ventricular hypertrophy in the precordial leads, about 90 per cent have left axis deviation, and approximately 70 per cent show "P" wave abnormalities.[15] Therefore, on electrocardiographic grounds, isolated hypoplasia of the right ventricle and tricuspid atresia cannot be differentiated. In Ebstein's malformation, however, which may present with similar clinical findings, left ventricular hypertrophy is quite rare and approximately 75 per cent show right bundle-branch block.[9]

Roentgenography

Teleroentgenograms. The cardiac silhouette is normal or shows moderate enlargement with no specific contour. Frequently left ventricular hypertrophy is present. In contrast to tricuspid atresia of which approximately 80 per cent have scanty pulmonary vascular markings, the markings were normal or slightly increased in 80 per cent of the five cases of isolated right ventricular hypoplasia (the present series, Gasul et al.[3] and Medd et al.[4]).

Angiocardiography. This shows an enlarged right atrium with early opacification of the left atrium due to the right-to-left shunt. The right ventricle is diminutive and may be difficult to define because of its superimposition on the early opacified left atrium. The left ventricle is hypertrophied and dilated.

Diagnosis

The diagnosis of this disorder should be suspected when cyanosis and signs of peripheral venous congestion predominate in a patient with left ventricular hypertrophy of uncertain etiology. Nonspecific systolic murmurs and gallop rhythms are frequent. The electrocardiograms show left axis deviation, left ventricular hypertrophy, and right atrial or combined atrial enlargement. The clinical diagnosis is confirmed by cardiac catheterization and venous angiocardiography. The presence of a mixed shunt at the atrial level in the absence of pulmonary hypertension, tricuspid or pulmonic valvular disease demonstrates the restriction to inflow caused by the hypoplastic right ventricle. This restriction is further suggested by the prominent "a" waves in the right atrial and ventricular pressure pulses.

Pulmonary atresia, Ebstein's malformation, tricuspid atresia, and Bernheim's syndrome must be considered in the differential diagnosis because of the findings of cyanosis, right-sided failure, left ventricular enlargement, and absence of distinctive murmurs. Pulmonary atresia can be excluded because a split second sound is present. As contrasted to the left ventricular hypertrophy in isolated right ventricular hypoplasia, the electrocardiogram in Ebstein's malformation shows right bundle-branch block in 75 per cent of cases. A definite differentiating point can be obtained only by recording intracardiac pressures and electrocardiograms simultaneously. In Ebstein's malformation right atrial pressure is recorded with right ventricular electrical potential. The clinical electrocardiographic and roentgenographic features of tricuspid atresia

are quite similar to isolated right ventricular hypoplasia. Cardiac catheterization readily differentiates the two, since the catheter cannot be passed across the atretic tricuspid valve. In Bernheim's syndrome signs of isolated right-sided heart failure are produced by stenosis of the cavity of the right ventricle by displacement of the interventricular septum. Cyanosis may be present due to peripheral stasis.[16] A history of preceding left ventricular disease is usually obtained.

Prognosis

It is noteworthy that the reported patients who died in infancy and the 2-month-old baby in this paper had patent but valvular competent foramen ovale. However, the cases of 4 to 39 years of age had atrial septal defect. Whether this is a fortuitous finding or is significant cannot be decided on the limited number of cases. The cause of death is severe intractable heart failure, which may be complicated by serious cardiac arrhythmias.

Treatment

Gasul and associates[3] reported the only case in which surgical palliation of the defect has been attempted. They anastomosed the superior vena cava to the right pulmonary artery in an effort to lower the load to the small right ventricle. Symptomatic improvement was evident, the peripheral arterial oxygen saturation rose from 80.6 to 89.4 per cent, the mean right atrial pressure dropped from 7 to 4 mm. Hg, and a left-to-right atrial shunt then predominated. However, no electrocardiographic or roentgenographic changes resulted, and the patient showed signs of congestive heart failure 9 months postoperatively. The authors stated that they are considering closure of the atrial septal defect.

Summary

With the rare exception of connective-tissue replacement of the right ventricular myocardium ("parchment heart"), underdevelopment of the right ventricle, as a clinical entity, has been related to tricuspid atresia or stenosis, pulmonary atresia and certain cases of transposition of the great vessels. This report is concerned with four cases, aged 2 months to 39 years, in which a diminutive right ventricle was not dependent on these factors. Three cases occurred in the same family and, in association with atrial septal defect, produced distinctive clinical and hemodynamic features. Right-sided heart failure predominated, dyspnea was mild to moderate, and cyanosis was present in association with clinical, electrocardiographic, and roentgenographic evidence of left ventricular enlargement. Cardiac catheterization and venous angiocardiography showed a bidirectional interatrial shunt, normal pulmonary arterial pressure, no pressure gradient across the pulmonic and tricuspid valves, and a diminutive right ventricle. Anastomosis of the superior vena cava to the right pulmonary artery and closure of the atrial septal defect may ameliorate the hemodynamic disturbance.

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Religio Medici

Think not thy time short in this World since the World it self is not long. The created World is but a small Parenthesis in Eternity and a short interposition for a time between such a state of duration, as was before it and may be after it.—SIR THOMAS BROWNE. *Religio Medici*, 1642. Edited by W. A. Greenhill, M.D., Oxon., London, MacMillan and Co., Limited, 1950, p. 230.

Production of Aortic Regurgitation by Unperforated Aneurysm of the Sinus of Valsalva

By SEYMOUR B. LONDON, M.D., AND ROSE E. LONDON, M.D.

RECENTLY we observed an elderly man with the classical features of aortic regurgitation and progressive left ventricular failure. Postmortem studies revealed the cause of the regurgitation to be an unperforated aneurysm of a sinus of Valsalva. Since aneurysm of the sinus of Valsalva is generally unrecognized until perforation occurs, the presence of aortic regurgitation, unexplained by other causes may be a diagnostic clue to this potentially lethal lesion. Surgical repair of the unperforated aneurysm may prevent the complications of aortico-cardiac fistula, subacute bacterial endocarditis, and cardiac failure.

Report of Case

A 76-year-old retired pharmacist 5 years prior to his terminal illness developed progressive cardiac disability, marked by dyspnea, orthopnea, and peripheral edema. The onset was associated with a partial paralysis of the left hand and leg. For 2 years prior to his death, he suffered bouts of severe chest pain over the right anterior chest, with radiation through both shoulders into the hands. The only significant past history was of a "chest condition," discovered over 40 years ago, for which restricted activity was advised.

On physical examination a nodding motion of the head was observed with each heart beat. The heart was enlarged with the apical impulse in the sixth left intercostal space at the anterior axillary line. The sounds were of good quality and the aortic second sound was louder than the pulmonic second sound. A loud diastolic murmur was heard over the precordium and was loudest at the aortic area, where a short systolic murmur was also heard. The blood pressure was 210/60. The lungs were resonant but many rales were present at both bases. No abdominal organs were palpable. The left arm and leg were weak, and there was moderate pitting edema of the legs. Peripheral pulsations were symmetrical and of a "water hammer" collapsing type, with capillary pulsations of the lips and nail beds.

Electrocardiograms showed marked left ventricular hypertrophy (fig. 1). X-ray of the chest indicated left ventricular enlargement; the aorta was tortuous but not dilated (fig. 2). The hemogram, Kahn test, urine examination, and serum electrolytes were normal.

For the 4 months prior to his death the patient experienced a relentless worsening course, marked by severe left ventricular failure responding poorly to salt restriction, digitalization, and diuretics. There were frequent attacks of severe prolonged chest pain attributable to coronary insufficiency and one episode associated with electrocardiographic evidence of anteroseptal myocardial infarction. He died during an acute bout of severe chest pain, orthopnea, and peripheral vascular collapse.

Autopsy showed an unperforated aneurysmal dilatation of the right sinus of Valsalva, measuring 2 by 1½ cm., which was eccentrically oriented, extending posteriorly behind the commissure of the right coronary and noncoronary leaflets (fig. 3). The aneurysm protruded down to the right atrium, indenting the tricuspid valve ring but not perforating through the thin glistening endothelium. There was no evidence of syphilis of the aorta. The aortic and mitral valves showed slightly nodular thickening commensurate with age but the chordae tendineae were thin. The endocardium of the left ventricle just beneath the valve of the right coronary sinus demonstrated thickening with formation of "diastolic pockets" (fig. 4) at several levels, pathognomonic of aortic valvular regurgitation.[1] Left ventricular hypertrophy was present. There was arteriosclerotic narrowing in all coronary vessels with occlusion of the left anterior descending artery and old and recent anterior myocardial infarction. There were chronic hyperemic changes in the lungs and abdominal organs compatible with congestive heart failure.

Discussion

Congenital aneurysm of sinus of Valsalva is a developmental defect due to the failure of the aorta to fuse firmly with the membranous ventricular septum at the annulus.[2, 3] The high intraluminal aortic pressure causes thinning and protrusion of the weakened structure. Since the location of the aortic annulus is intracardiac, aneurysms of the different sinuses bear unique relationships,[4, 5] the

From the Miami Heart Institute, Miami, Florida.

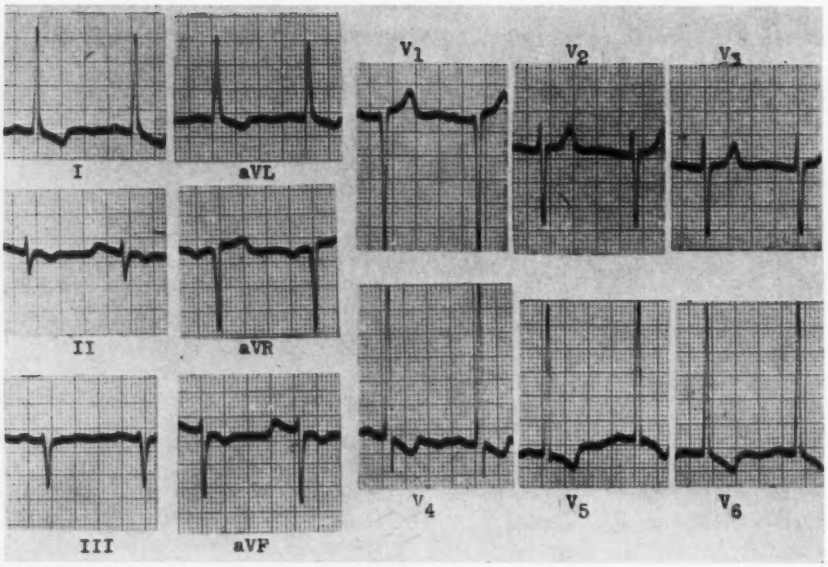

Figure 1

Electrocardiogram demonstrating left ventricular hypertrophy.

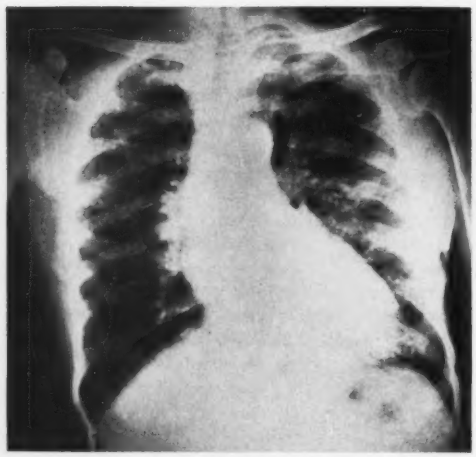

Figure 2

Teleroentgenogram of chest. The mediastinum is not remarkable. The left ventricle is prominent.

right coronary sinus being related to the right ventricle, and the noncoronary sinus to the right atrium. The left coronary sinus, which generally is not involved in congenital aneurysm, is encased in the left ventricle.

Figure 3

Postmortem view of open heart at the level of the base of the aorta, aortic valves, and left ventricle. The arrow above the aneurysm and the clamp retracting the normal thin valve of the right coronary sinus demonstrate the eccentric position of the aneurysm. The superior margin of the aneurysm formed by the aortic endothelium projects "self-like" over the aneurysm. The wall of the left ventricle (lower right margin of the picture) is hypertrophied.

Perforated aneurysm of the sinus of Valsalva has received considerable attention recently because of the dramatic nature of the

Figure 4

Endothelial pockets formed by the regurgitant jet are indicated by the arrow. The normal commissure between the right coronary sinus and posterior (noncoronary sinus) and the mouth of the aneurysm is seen above the arrow.

illness,[6-8] the outstanding physical signs, the confirmation by contrast aortography, and the recent feasibility of surgical repair.[9, 10, 12] On the other hand, unperforated aneurysm of the sinus of Valsalva has received scanty mention because of the lack of characteristic features. Outstanding in our case was the classical aortic regurgitation, manifested by clinical, electrocardiographic, and x-ray findings and confirmed by postmortem studies. While there has been occasional association[13-15] of aortic regurgitation with unruptured aneurysm of the sinus of Valsalva of the congenital type, the significance and the mechanism of production of aortic regurgitation in this situation have not been elucidated. Our concept based on the anatomic findings in this case, is that the failure of the aorta to fuse to the annulus fibrosis not only provides a weakened area, so that aneurysms can be produced, but that the annulus itself is not supported by the suspending action that the aorta normally provides. As the high intraluminal pulse pressure is exerted against the weakened wall, aneurysmal formation occurs with protrusion into the adjacent structure. Since the annulus is unsupported, it eventually is involved in this protrusion with the result that buckling of the rim occurs. This interferes with appo-

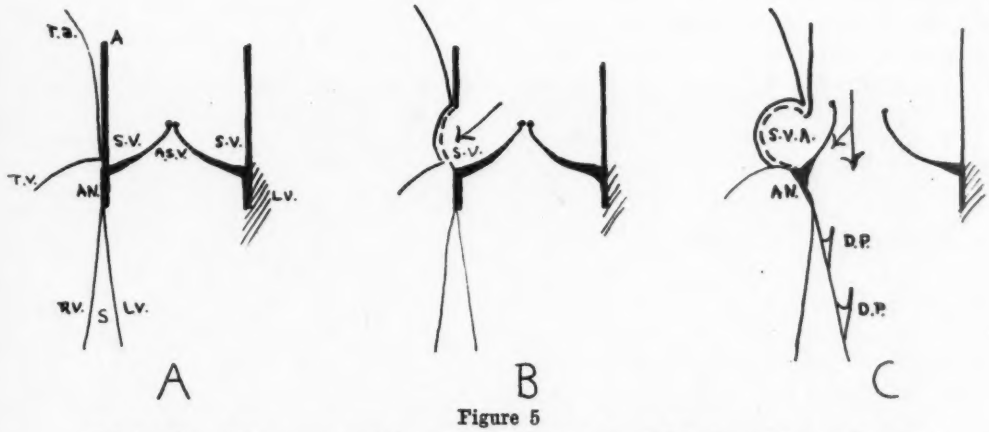

Figure 5

Relationship of the unperforated aneurysm of the sinus of Valsalva to the annulus of the aortic ring. A. *Normal relationships of sinus of Valsalva to adjacent structures at the annulus of the aorta.* B. *Congenital weakness of sinus of Valsalva area is due to failure of fusion of aorta to annulus. Arrow indicates direction of pressure against the weakened wall.* C. *Protrusion of aneurysm (S.V.A.) into right atrium and base of tricuspid valve; displacement of annulus laterally and failure of apposition of valves causes regurgitant jet; production of endothelial diastolic pockets (D.P.) on the ventricular septum results. A, aorta; Ann, annulus; A.S.V., aortic semilunar valves; l.v., left ventricle; r.a., right atrial wall; r.v., right ventricular wall of septum; S, septum; S.V., sinus of Valsalva; T.V., tricuspid valve.*

sition of the valves and leads to aortic regurgitation (fig. 5).

The clearly audible aortic second sound despite clinical aortic regurgitation is consistent with the normal, pliable valves found at autopsy and serves as a distinguishing feature from rheumatic valvulitis and calcific aortic disease, in which the valve structure is fixed and deformed, with loss of the aortic second sound. Syphilis of the aorta results in separation of the commissure with resultant aortic regurgitation. The second aortic sound eventually disappears when the valves, which are otherwise normal, are unable to achieve any approximation.

Since aortography[15-17] clearly identifies the presence and magnitude of the aneurysm of the sinus of Valsalva, it serves ante mortem as the single diagnostic criterion in distinguishing the etiology of aortic regurgitation. Clinical suspicion, however, should be aroused in all cases of aortic regurgitation in which the etiology is not obvious.

Conclusions

A case report is presented of an elderly man with severe aortic regurgitation and cardiac failure in which the etiology, revealed by postmortem studies, was due to the effects of unperforated aneurysm of the sinus of Valsalva.

The mechanism of production of aortic regurgitation due to aneurysm of the sinus of Valsalva is discussed.

Unperforated aneurysm of the sinus of Valsalva should be considered as a possible cause of aortic regurgitation and cardiac failure when the etiology has not been established. The usefulness of contrast aortography is suggested in those cases in which surgical repair might be desirable.

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Roentgen Television Study of Cardiac Calcifications

By N. P. G. Edling, M.D.

IN HEART SURGERY of mitral and aortic stenosis the presence of calcifications in the ostial rings and valves makes the management more difficult. The knowledge of the presence of calcifications preoperatively is therefore important.

Our methods for their visualization used up to now have their advantages and disadvantages. Screening reveals the characteristic movements of the deposits but requires full adaptation of the eye. Heavily exposed films, with very short exposures, can demonstrate the calcifications in different views but they may be overlooked if poor technic is used, or become unsharp in frequent heart pulsations. Tomography at small angles and short exposure time (Lindblom 1955) reveals even small calcifications. The method is time-consuming compared with conventional heart radiography and being performed in oblique prone position, it is often too tiring for many heart patients.

Since the introduction of the image intensifier with television the diagnostic situation is simpler. The apparatus used for the present study is a Siemens image intensifier and a Fernseh Orthicon television camera fitted with a conventional receiver. This procedure includes the advantages but not the disadvantages of the above methods. The patient may be examined in sitting or lying position in daylight. The time needed for the examination is about the same as for ordinary screening.

The calcifications are visible with great evidence on the television screen (figs. 1 and 2). For study of the mitral ostium, frontal and lateral views are sufficient; for the aortic os-

From the Roentgendiagnostic Department B, Karolinska sjukhuset, Stockholm, Sweden.

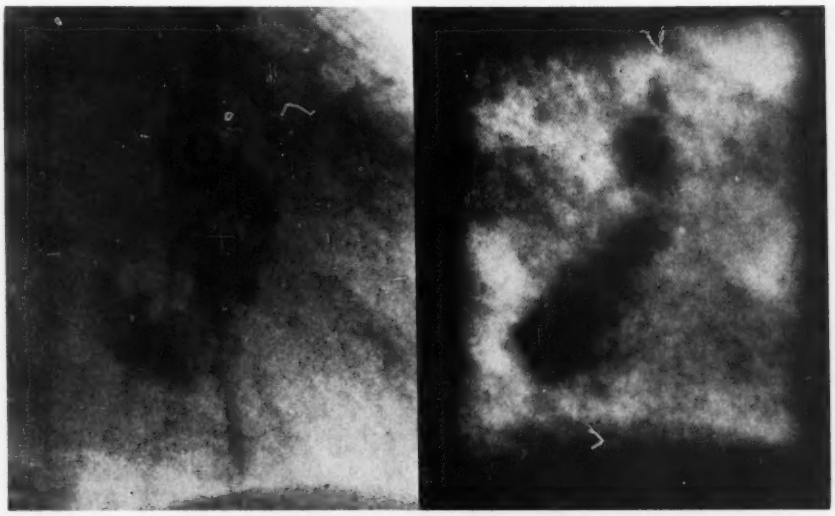

Figure 1

Calcifications of mitral ring. Frontal views. Left. *Plain radiographic in erect position of the patient.* Right. *Photograph of television picture in supine position of the patient.*

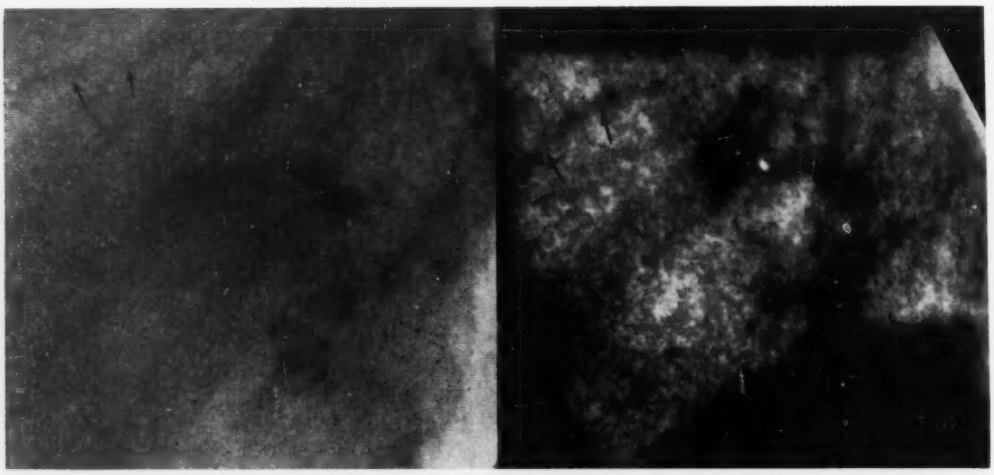

Figure 2

Calcifications of mitral ring and left coronary artery (arrows). Lateral views. Left. *Plain radiograph in erect position of the patient.* Right. *Photograph of television picture in lying position of the patient.*

tium, slight rotation to the left and a lateral position are required. The movements of the calcifications, not only identify and differentiate them from calcifications of the lungs and ribs, but also facilitate their recognition when they are small or of poor density. In questionable cases the radial pulse indicates the rate of the movements; difficulties may occur in a slow, perpetual arrhythmia. Differences in the extent of the movements of the calcified area may suggest localization to the ring, or to the valves.

In addition, calcifications of the coronary arteries are also easily observed, due to their movements. The left artery is generally mostly affected and the changes are visible in slight rotation to the left and in the lateral view (cf. fig. 2).

With some experience it should be possible also to exclude cardiac calcifications of clinical importance by means of the method.

Summary

A study on roentgen television of cardiac calcifications is reported.

Reference

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Direct Communication of a Pulmonary Artery with the Left Atrium

An Unusual Variant of Pulmonary Arteriovenous Fistula

By Russell V. Lucas, Jr., M.D., George W. Lund, M.D., and Jesse E. Edwards, M.D.

THE CLINICAL INTEREST evidenced in recent years in pulmonary arteriovenous fistula results in part from the availability of curative surgical procedures for its treatment. Since over 140 cases of this condition have been reported in recent years, it can no longer be considered rare. In pulmonary arteriovenous fistula a direct communication exists between a large pulmonary artery, on the one hand, and a pulmonary vein on the other. Therefore, pulmonary arterial blood low in oxygen content is delivered without further oxygenation through the fistula to the left atrium. The result of this right-to-left shunt may be cyanosis, clubbing, dyspnea, polycythemia, and the opportunity for paradoxic embolization to the systemic circuit. The brain seems particularly prone to receive such emboli. Pulmonary arteriovenous fistulas range in size from very small, without clinical findings, to very large communications with prominent clinical manifestations. This report presents the case of a patient with an unusual form of pulmonary arteriovenous fistula, namely, direct communication of the right lower pulmonary artery with the left atrium. This anomaly had evidently been responsible for a large right-to-left shunt, as cyanosis had been a prominent clinical sign in this patient who succumbed to a cerebral abscess.

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Supported by research grant no. H-5694 of the National Heart Institute, U. S. Public Health Service.

Case Report

Clinical Findings

A 3-year-old, cyanotic white female child awoke one evening complaining that her left arm hurt. Shortly thereafter, the arm began to shake and in 1 hour she was unable to move it. Subsequently, several mild convulsive movements of the left arm and left leg occurred. The past history revealed that a normal delivery had followed a normal pregnancy. Growth and development had been normal but the patient was noted to be "dusky" at 1 year of age. No other symptoms were referable to the cardiopulmonary system.

Physical examination revealed a cyanotic child who was listless, but could be aroused. The body temperature was 104 F. by rectum. Clubbing of the fingers and toes was present. A soft, systolic murmur was heard over the base of the heart. The cardiac rate and rhythm and blood pressures were within normal limits. The only abnormal neurologic findings were a left knee jerk more active than the right and absent abdominal reflexes.

Laboratory studies revealed a hemoglobin of 18.5 Gm. per 100 ml., a hematocrit level of 62 per cent, and a total leukocyte count of 8,600 per cu. mm. The differential leukocyte count in percentages was as follows: neutrophils, 71; lymphocytes, 25; monocytes, 3; and eosinophils, 1. The sedimentation rate was 15 mm. per hour. No remarkable findings were observed in the urinalysis, blood chemical or spinal fluid studies. Cultures of the urine and of the throat revealed no significant features. A Mantoux tuberculin test gave negative results. An electroencephalogram suggested a localized lesion in the right cerebral hemisphere.

An electrocardiogram (fig. 1) revealed left axis deviation and evidences of left ventricular hypertrophy and left atrial enlargement. A thoracic roentgenogram (fig. 2) suggested slight generalized cardiac enlargement with prominence of the left atrium and minimal right ventricular enlargement. A rounded density approximately 3 cm. in diame-

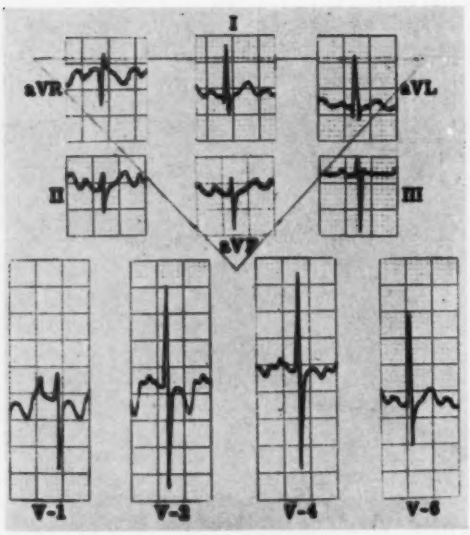

Figure 1

Electrocardiogram taken during initial period of hospitalization. The pertinent findings include left axis deviation of the QRS complex and evidences of left ventricular hypertrophy and left atrial enlargement.

ter, which could not be separated from the cardiac shadow, was present just to the right of, and anterior to, the spine. The pulmonary vascular markings were interpreted as normal.

The admitting diagnosis was congenital cardiac disease with right-to-left shunt and cerebral abscess. Penicillin and chloramphenicol were administered. On the second day of hospitalization the temperature had fallen below 100 degrees and remained normal thereafter. The neurologic symptoms cleared during the following 12 days. Results of repeated blood counts and urinalysis were normal throughout 12 days of antibiotic therapy. A thrombotic or embolic episode of the brain was therefore considered more likely than an infectious one. The antibiotics were discontinued. On discharge from the hospital, on the fourteenth day, the patient's neurologic findings were normal. She was to return in 1 month for angiocardiographic confirmation and treatment of a clinically suspected pulmonary arteriovenous fistula.

Three weeks following discharge from the hospital the patient suddenly became febrile and comatose. The spinal fluid contained 70,000 polymorphonuclear leukocytes per cubic millimeter. Despite intensive antibiotic and supportive treatment, the patient died 6 hours following the onset of the terminal illness.

Figure 2

Left. *Posteroanterior thoracic roentgenogram taken during initial period of hospitalization. The pulmonary vascular markings are within normal limits. The bulge along the left cardiac border suggests left atrial enlargement. A rounded density is seen to the right of the spine in the region of the right pulmonary hilus. This density could not be separated from the cardiac shadow but was thought to represent a pulmonary arteriovenous fistula.* Right. *Lateral roentgenogram. The rounded density in question lies behind and inferior to the position of the left atrium.*

Pathologic Findings

The pertinent findings were restricted to the central nervous and cardiovascular systems. Meningitis was associated with a solitary abscess in the right cerebral hemisphere containing 60 ml. of purulent material. Culture of this material revealed *Pseudomonas aeruginosa*.

Study of the cardiovascular system revealed that the pulmonary trunk and the aorta were normally interrelated. The wall of the pulmonary trunk was thick, being almost as thick as the wall of the aorta.

The origins of the right upper and lower pulmonary arteries and of the left pulmonary artery each showed a zone of moderate stenosis beyond which the walls approached normaley in thickness (fig. 3, left).

The left lung and the course of the left pulmonary artery were normal. The left pulmonary veins, two in number, followed a normal course to the left atrium. The right lung had only one lobe, the upper, which filled the right hemithorax. The one vein from this lobe followed the course of the right upper pulmonary vein and entered the left atrium normally.

The right pulmonary artery bifurcated into upper and lower branches. The upper branch entered the single lobe of the right lung. The right lower pulmonary artery led into the left upper aspect of a thin-walled sac-like structure

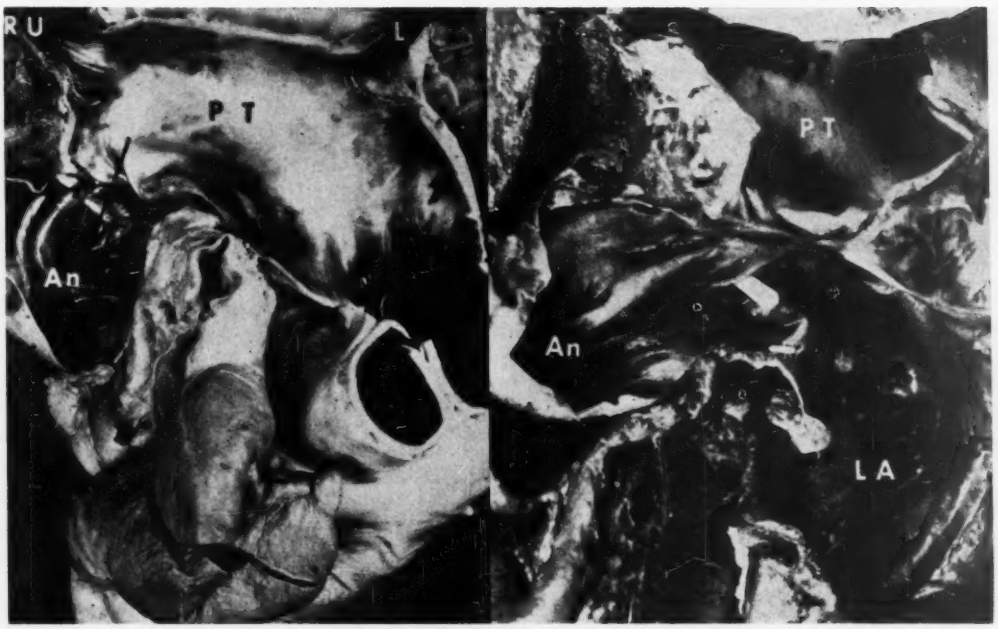

Figure 3

Left. *Interior of pulmonary arterial trunk (PT). It is dilated and thick-walled. Moderate stenosis is present at the origin of the left pulmonary artery (L), right upper pulmonary artery (RU) and the right lower pulmonary artery (line). Direct communication (line) exists between right lower pulmonary artery and the thin-walled aneurysmal sac (An). Communication of the latter with the left atrium is illustrated in* Right. Right. *The communication of the right lower pulmonary artery and aneurysmal sac (An) is again seen. The latter structure indents the adjacent pulmonary tissue and communicates directly with the left atrium (LA). The probe identifies the normal junction of the right upper pulmonary vein with the left atrium.*

measuring about 2.5 by 2 cm. in diameter. This structure, which lay to the right of the left atrium, was imbedded in a concavity of the medial aspect of the adjacent enlarged single right pulmonary lobe. The lower medial aspect of the sac-like structure, which received the right lower pulmonary artery, communicated with the left atrium at the expected location of the ostium of the right lower pulmonary vein (fig. 3, right). Because of the latter connection, on the one hand, and the aforementioned connection with the right lower pulmonary artery, on the other, the sac-like structure provided an unbroken connection between the right lower pulmonary artery and the left atrium (fig. 4).

The right ventricular wall was of normal thickness, whereas the left ventricular wall was considered mildly hypertrophied as its wall measured about 1.4 cm. in thickness. The left atrial and ventricular cavities did not appear enlarged.

Discussion

As in the case reported, communication between a pulmonary artery and the left atrium is to be considered a form of pulmonary arteriovenous fistula. In the usual form of this condition, pulmonary parenchyma is formed, and the abnormal communication lies within pulmonary tissue. In our case, absence of the middle and lower lobes in association with the fistula described suggests that the primordia of these lobes had at one time been present but that while the vascular connections persisted, the parenchyma failed to develop. Enlargement of the capillary bed of the anomalous area of the right lung may be represented by the sac-like structure described. The arterial connection with this structure is

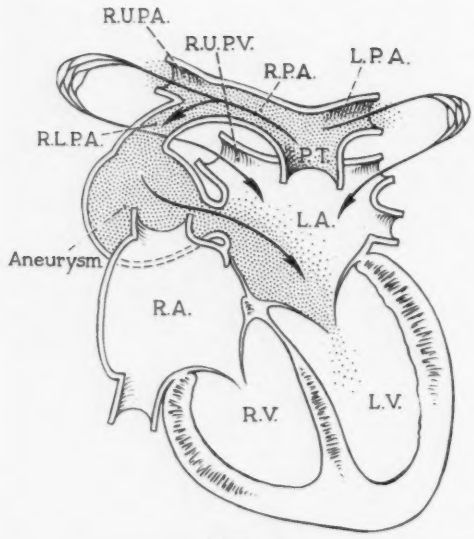

Figure 4

Diagrammatic representation of the anomaly, direct communication of the right lower pulmonary artery with the left atrium. The central right-to-left shunt resulting from this anatomic arrangement is demonstrated.

representative of the early arterial system in this area, while the connection with the left atrium may be looked upon as representing the right lower pulmonary vein.

Since direct communication of the right lower pulmonary artery with the left atrium appears to represent a form of pulmonary arteriovenous fistula, a brief consideration of this larger category of congenital disease is in order. The recent excellent reviews on pulmonary arteriovenous fistula by Stringer and associates[1] and by Muri[2] have well summarized the cases reported in the literature. Both reviews found that about 50 per cent of cases of pulmonary arteriovenous fistula are associated with telangiectasis of the skin and mucous membranes. Cyanosis and clubbing of the digits were very frequent. Dyspnea was less common, and was manifested relatively late. Congestive heart failure was unusual. Neurologic symptoms were frequent, occurring in 41 of the 140 cases reviewed by Stringer, including five patients who succumbed with cerebral abscess. A systolic cardiac murmur was present in about half the patients. Hemoglobin and hematocrit values were commonly elevated. Despite frequent and pronounced cyanosis, cardiomegaly either by roentgenographic or by electrocardiographic criteria was unusual.

An insight into the natural history of the anomaly may be gained from Muri's review of 117 cases of pulmonary arteriovenous fistula. Of the 50 patients who did not have corrective surgery, 20 succumbed, including five with cerebral abscess and seven with rupture of the fistula. Primary surgical mortality in the 67 patients who had received surgical correction was 7 per cent.

The diagnosis of a pulmonary arteriovenous fistula may frequently be made from the thoracic roentgenogram by visualization of a mass either near the pulmonary hilus or in a peripheral pulmonary field. This diagnosis may be confirmed by venous angiocardiography, which demonstrates the shunt from the pulmonary arterial to the pulmonary venous systems.

Friedlich and associates[3] reported on the hemodynamic findings in four patients with pulmonary arteriovenous fistulas (one patient with direct communication between the right pulmonary artery and the left atrium). Normal pulmonary arterial pressure was universal. Peripheral arterial oxygen desaturation resulted from a right-to-left shunt which was calculated to vary from 42 to 76 per cent of the right ventricular output. Despite this large diversion of blood, cardiac output was normal in three patients and only slightly above normal in the fourth.

Estimates of resistance of the fistulous tract alone and of the pulmonary vascular bed, exclusive of the fistula, were made by the aforementioned investigators. Resistance in the fistula was equal to that seen in the normal pulmonary vascular bed, whereas the vascular resistance in the nonfistulous part of the pulmonary vascular system was about twice normal. Since the normal and anomalous pulmonary circuits are in parallel, this difference of resistance favors flow through the low re-

sistance (anomalous) channel. The common phenomenon of delay in appearance of cyanosis until adolescence or adult life is perhaps on a basis of acquired increasing resistance in the nonfistulous part of the pulmonary vascular bed.

The type of pulmonary arteriovenous fistula wherein the pulmonary artery communicates directly with the left atrium is a rare abnormality. Only two other cases are known to the authors. One of these occurring in a 15-year-old boy was reported by Friedlich and associates[3] as well as by Sloan and associates.[4] In this patient, cyanosis was first apparent at 5 years of age and gradually increased in intensity. Clubbing of the digits and polycythemia were associated. A pulsating hemangioma was present on the forehead. Cardiac catheterization revealed a normal right ventricular output but it was estimated that 71 per cent of this output was shunted into the systemic circulation (via the left atrium). The electrocardiogram showed right axis deviation, and the thoracic roentgenogram revealed a normal cardiac shadow with no abnormalities of the pulmonary fields. Angiocardiography demonstrated a right-to-left shunt in close proximity to the right pulmonary hilus.

At operation performed on this patient by Dr. Alfred Blalock, it was reported that one of the branches of the right pulmonary artery, which measured about 1 cm. in diameter, extended posteriorly and communicated directly with the left atrium. When the anomalous vessel was interrupted, the patient's cyanosis disappeared immediately.

A second case of communication of a pulmonary artery with the left atrium was reported in the Case Records of the Massachusetts General Hospital.[5] A 45-year-old woman was admitted with mental confusion. The history revealed that she had been cyanotic for at least 7 years. Examination revealed generalized cyanosis but no clubbing of the digits. Congestive heart failure and atrial fibrillation were apparent. The electrocardiogram revealed evidence of right ventricular hypertrophy and right bundle-branch block and evidence for anterior myocardial infarction. Supportive treatment failed and the patient succumbed. On pathologic examination there was a direct communication of the right pulmonary artery to the upper portion of the left atrium, the circumference of the anomalous channel being 2.5 cm. In addition, there were cerebral emboli and infarcts, emboli in the posterior descending coronary artery, and splenic infarcts.

The clinical findings in patients with direct communication of a pulmonary artery with the left atrium differ only in degree from those in the more common types of pulmonary arteriovenous fistula. The large diameter of the fistulous channel in this type of connection and its short course results in a low resistance in the fistulous channel and facilitates a large right-to-left shunt.

The cerebral abscess present in our case and its common occurrence in intrapulmonary types of arteriovenous fistula is considered a complication of the circumstances of a central right-to-left shunt. In regard to this particular complication, pulmonary arteriovenous fistula is similar to the many forms of intracardiac malformations that are associated with a right-to-left shunt.[6, 7]

The electrocardiogram of the patient whose case is here reported is of interest. It revealed evidence of left atrial enlargement, left axis deviation, and left ventricular hypertrophy. While the electrocardiogram has not been stressed in other reports on pulmonary arteriovenous fistulas, it has usually been described as normal. In our case, the findings of left atrial and left ventricular hypertrophy may, in fact, be due to the large right-to-left shunt that had apparently been present with a resultant augmentation of blood flow through the left atrium and left ventricle.

It is apparent from the study of the pathologic material in our case that surgical ablation of the fistulous channel at an appropriate time would have resulted in elimination of the right-to-left shunt and would have prevented the fatal complication, the cerebral abscess.

Summary

Direct communication of a pulmonary artery with the left atrium is described and considered a variant of pulmonary arteriovenous fistula.

A 3-year-old girl presented with clinical evidence of a lesion of the central nervous system. The history revealed that she had been cyanotic and had had clubbing of the digits and polycythemia. A rounded mass was noted in the region of the right pulmonary hilus in the posteroanterior thoracic roentgenogram. A pulmonary arteriovenous fistula was suspected, but the patient succumbed with a cerebral abscess before definitive diagnostic studies and therapy were undertaken.

Anatomic examination revealed an unusual variant of pulmonary arteriovenous fistula, namely, direct communication of the right lower pulmonary artery with the left atrium and absence of the middle and lower lobes of the right lung.

It is important that pulmonary arteriovenous fistulas be suspected clinically, since definitive diagnosis and therapy are now possible. While the hemodynamic effects of this type of lesion are usually not severe, untreated patients suffer a high morbidity and mortality through systemic arterial oxygen desaturation, paradoxic embolization, cerebral abscess, and rupture of the fistula.

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From the materialistic and the energetic standpoint alike, carbon, hydrogen, and oxygen, each by itself, and all taken together, possess unique and preeminent chemical fitness for the organic mechanism. They alone are best fitted to form it and to set it in motion; and their stable compounds, water and carbonic acid, which make up the changeless environment, protect and renew it, forever drawing fresh energy from the sunshine. —Lawrence J. Henderson. *The Fitness of the Environment.* New York, The Macmillan Co., 1924, p. 248.

SPECIAL ARTICLE

Dietary Control of Serum Cholesterol in Clinical Practice

By NORMAN JOLLIFFE, M.D.,† ETHEL MASLANSKY, M.S., FLORENCE RUDENSEY, R.N., B.S., MARTHA SIMON, M.S., AND ALICE FAULKNER, M.S.

THE RELATION of lipids in the diet to blood lipids and their significance in the etiology of atherosclerosis is subject to considerable differences of opinion. The Central Committee for Medical and Community Programs of the American Heart Association, through the Board of Directors, revised a recommendation made to them in 1957,[1] and now considers that "reduction or control of fat consumption under medical supervision with reasonable substitution of polyunsaturated for saturated fats is recommended as a possible means of preventing atherosclerosis and decreasing the risk of heart attacks and strokes."[2] The purpose of this article is to help implement the recommendation of the American Heart Association by providing the necessary practical dietetic information for the practicing physician and cardiologist in the dietary control of serum cholesterol and other lipid fractions in those instances in which they consider dietary control "indicated."

Diets for the control of hypercholesteremia have been conveniently divided into two major types: the "Prudent Diet Pattern" and the "Therapeutic Vegetable Oil Diet Pattern."

Prudent Diet Pattern

The "Prudent Diet" pattern was devised by the senior author in 1956 and used experimentally on a few subjects. It was put into effect on a larger scale in 1957 when the Diet and Coronary Heart Disease Study Project of the Department of Health, City of New York, was initiated.[3] The "Prudent Diet" is one recommended for use to the general public and furnishes the family an adequate, well-balanced diet pattern for all normal adults and, with modification of the milk allotment, for children after infancy.[4, 5] This diet pattern is nutritionally adequate and meets the specific nutrient requirements of the Recommended Dietary Allowances of the Food and Nutrition Board of the National Research Council. It is palatable and consists of acceptable American foods commonly available in every community. In addition, it is made up of foods listed in the normal diet pattern recommended by the U. S. Department of Agriculture in their Home Economics Research Report Number 3. In practice,[3] we have found that this diet pattern furnishes approximately 30 per cent of its calories as fat, which for a caloric intake of about 2,300 (the maintenance level for the average normal weight urban man in his 50's) will supply about 75 Gm. of total fat. Of this total, about 20 Gm. are saturated fatty acids, 25 Gm. monounsaturated, and 30 Gm. polyunsaturated, yielding a polyunsaturated fatty acid/saturated fatty acid ratio (the P/S ratio) of 1.5. Theoretically, if our subjects followed our prescription rigidly, this ratio would be about 1.8 to 2.0. For a 1,800 caloric diet (the maintenance level for the average normal weight urban woman in her 50's) this diet will supply a total of about 60 Gm. of total fat, of which 16, 20, and 24 Gm. are saturated, monounsaturated, and polyunsaturated, respectively.

We have devised a prudent diet pattern

From the Bureau of Nutrition, Department of Health, New York, New York.

†Deceased.

for two types of individuals, (a) the "Prudent Diet" for those of normal weight without a weight problem and whose normal appetite can be depended upon to regulate their total caloric intake; (b) the "Prudent Reducing Diet" for overweight subjects who must be reduced and then maintained at the lower desirable weight. This diet requires that the quantity of food be prescribed in terms of common household measurements. At the end of weight reduction, it can be converted to the prudent diet by the addition of 45 Gm. of vegetable oils and, if desired, 10 Gm. of a linoleate-rich margarine* as well as bread, fruit, cereals, and vegetables in amounts needed to add sufficient calories to maintain weight at the reduced desired level.

The "Prudent Diet" pattern is practical in that it can be followed indefinitely by the majority of motivated subjects. It has been effective in lowering the serum cholesterol in the majority of our subjects: about 80 per cent of those with control levels in the upper tertile (270 mg. per cent and over), 60 per cent of those in the middle tertile (230 to 269 mg. per cent), and 30 per cent of those in the lowest tertile (under 230 mg. per cent). It is thus effective in lowering the serum cholesterol in about 60 per cent of people with serum cholesterol levels above 230 mg. per cent. The effectiveness of this composite lowering of all subjects is shown in figure 1, which represents the course of the serum cholesterol of 97 men of normal weight aged 50 to 59 years during the control period and at the end of 6 months on the diet.[3, 6] There is a fall in cholesterol from the control level of 253 to 224 mg. per cent after 6 months ($t = 5.16$, significant beyond the 1-per cent level). The figure further demonstrates the fall in cholesterol by tertiles. In the highest third, 34 men dropped from 298 to 253 mg. per cent; in the middle third, 32 men dropped from 249 to 224 mg. per cent, while in the lowest third, 31 men dropped from 207 to 191 mg. per cent after 6 months on the "Prudent Diet." The fall in each tertile is significant beyond the 1-per cent level. Those patients with positive diagnoses of coronary artery disease responded like those with no coronary artery disease but with similar control cholesterol levels.

The number of subjects have now been extended to about 300 men[7] and the period of observation has been extended up to 3 years, with the serum cholesterol levels showing no tendency to rise with time with most subjects except when the subject, either deliberately or carelessly, broke the diet. It is surprising how many subjects, after a fall in serum cholesterol as a result of the "Prudent Diet," deliberately break the diet to see if a rise in cholesterol results. It does.

The instructions for the "Prudent Diet Pattern" designed for people of normal weight without a weight control problem follow:

1. Consume adequate amounts of high-grade protein foods at each meal. The sources for these include cottage cheese (preferably skim-milk cottage cheese), fat-free milk, chicken, turkey, veal, leaner cuts of beef, mutton, lamb, pork, fish, seafood, and egg whites. All visible fat should be removed from the meats and poultry.

Remember, there are 21 meals each week. Therefore, from this list, include fresh or

*The senior author has proposed to the Food and Drug Administration that, in the interest of easy consumer identification, a margarine, shortening, or other product composed chiefly of fats and oils be allowed to carry on their label the term "linoleate-rich" or some other appropriate term provided that the product contains over 25 per cent of cis-cis linoleic acid (or its biologic equivalent) and a P/S ratio of at least 1.25. Margarines meeting these specifications generally available at the present time include (1) Emdee, made by Pitman-Moore Company, available in drug stores, at a recommended price of $1.00 per pound, (2) Mazola Margarine, made by Corn Products Company, available at grocery stores at a recommended price of 41c per pound, (3) Fleischman's Sweet (Unsalted) Margarine (wrapped in a green label), made by Standard Brands, Inc., available in the frozen-food section of grocery stores, and selling at a recommended price of 49c per pound. These same companies may make other brands of margarines that do not meet these requirements and are not recommended for the prudent diet.

canned fish or seafood in at least five meals each week. Lunch is a good time for this. Do not be limited to the leaner fish but include fat fish as well, as they are good sources of polyunsaturated fatty acids. Bake, roast, broil, or boil meats and poultry. Fish, veal, and chicken may be fried in a vegetable oil rich in polyunsaturated fatty acids (corn, cottonseed, safflower, soybean, sunflower). Use veal or poultry in four meals each week or oftener. Use 3-oz. servings for women, 4-oz. servings for men, of beef, lamb, mutton, and pork—a combined total of not more than 12 oz. for women and 16 oz. for men each week. For the other eight meals each week use cottage cheese or egg whites, an occasional serving of liver, or additional servings of fish, seafood, or poultry. Unless otherwise instructed, you may use up to four whole eggs each week. You may also use whole milk for coffee but otherwise restrict the use of milk to non-fat varieties, such as fresh or reconstituted skim milk, fat-free buttermilk, or evaporated skim milk. When instructed, you may emulsify a vegetable oil rich in polyunsaturated fatty acids with your skim milk by use of a high-speed electric mixer.[8]

2. A total of 1½ oz. (45 ml.) of vegetable oil rich in polyunsaturated fatty acids should be consumed daily. Most patients prefer to use about ½ oz. in food preparation and consume a minimum of 1 oz. of the oil at the table each day. This may be used in salad dressings and on vegetables, emulsified in milk, or added to cereals or soups. In addition, you may use a 10-Gm. pat of a recommended margarine rich in liquid vegetable oil daily as a table spread. When a solid fat is preferred in cooking or baking, use a recommended margarine rich in liquid vegetable oil, preferably one with a P/S ratio of 1.5 or higher. Never use the conventional partially hydrogenated types of margarines, cooking fats, or butter. Do not reuse and do not heat it to the smoking point.

3. Do not eat the following: butter, cream, whole milk, and ice cream; conventional partially hydrogenated margarine, shortening, and lard; foods containing these in large amounts, such as most cakes and pastries. In place of butter and ordinary or partially hydrogenated margarine, use a recommended margarine rich in liquid vegetable oil; in place of shortening, use either a vegetable oil rich in polyunsaturated fatty acids or a recommended margarine or shortening rich in liquid vegetable oil*; in place of cream use an emulsion of a vegetable oil rich in polyunsaturated fatty acids.

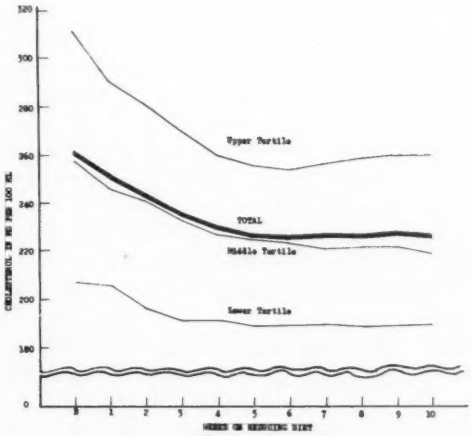

Figure 1

Ninety-seven men of normal weight, 50 to 59 years old, on prudent diet to 6 months. Total and tertiles.

4. Balance the diet by consuming adequate amounts of vegetables, fruits, nuts, bread, and cereals.

More than 4 years' experience with more than 600 men and their wives shows the following to be the most common difficulties encountered by our subjects in adhering to the "Prudent Diet": 1. Giving up pastries with a high content of saturated fat, such as Danish pastry, coffee cake, pound cake, "plain" cake, cookies, and pies. This prohibition is a real deprivation for many people and causes the most frequent difficulty. These products need not be prohibited for the person whose wife is willing to make them with vegetable

*Solid shortenings rich in liquid vegetable oil are not, at this writing, available for use by the general public.

oil or a recommended margarine or shortening —one containing a P/S ratio of about 1.5 or higher. These shortenings, in the form of a liquid vegetable oil containing an emulsifier, are on the market and available to the commercial baker, and produce in many instances pastry products with eating qualities similar to those made with conventional solid shortenings. At this time, the Food and Drug Administration has not permitted industry clearly to identify these products for the consumer.

If the government regulatory agencies would permit factual labeling of this improved type of product by the distributors, the commercial bakers, in cooperation with the manufacturers of shortening, could make this type of baked goods readily available and identifiable at the point of sale. This might be as valuable to the public health as the bakers' contribution in cooperating with the bread-enrichment program. Recipes for the use of vegetable oils in cooking and baking have been developed by the major vegetable oil companies and may be obtained gratis from them. Since most modern housewives, however, do not or will not do their own pastry baking, persons following this diet are limited to angel food cake, sponge cake, Holland honey cake, almond macaroons, and the few other low-fat baked goods that are commercially available. 2. Limiting the size of portion and the frequency of serving of all flesh products, especially beef, mutton, and pork, which contain the greatest amount of saturated fats. Many men in our affluent society have become accustomed to consuming 8-, 10-, and 12-ounce portions of these products. In a balanced diet, containing adequate calories, no normal person needs servings of animal flesh greater than 3 or 4 ounces daily, especially when skim milk and cottage cheese are also included. 3. Prohibition of ice cream is a deprivation for many persons, although this ranks well below the first two complaints listed. Here, water ices and sherbets are the best substitutes in states prohibiting imitation ice cream. In those states where this product is legal, frozen desserts imitating ice cream in appearance, taste, and consistency can be made with liquid vegetable oils in place of butter fat. This latter product is permitted in the prudent diet of the persons without a weight problem. 4. Restaurant meals may present difficulty for some people but this difficulty is more apparent than real. In restaurants where the food is prepared to order, no problem exists. In restaurants and cafeterias, where the food is prepared on a large scale, the entree chosen should be fish, seafood, or poultry, which should be boiled, broiled, or baked. The dessert should be limited to fruit. 5. Prohibition of hard cheeses of all varieties is a minor difficulty for a few people. For those who must have hard cheese occasionally, one ounce may be substituted for 2 ounces of the beef, mutton, or pork allowance. 6. The prohibition of butter, cream, and whole milk has presented no difficulties. Butter is one of the easiest foods to replace in the dietary, since so many substitutes are available, e.g., the recommended margarines, mayonnaise, and cottage cheese spreads moistened with skim milk or skim milk filled with vegetable oil. For the occasional subject with a peptic ulcer, emulsifying the vegetable oil in skim milk is satisfactory.

The Prudent Reducing Diet (for Persons Who Are Overweight)

People who are overweight due to excess fat or those who have been overweight and are attempting to maintain their lowered weight must, as a rule, be given diets in which the amount of food is detailed in standard portions. For these people, we have devised a "Prudent Reducing Diet" and a "Prudent Maintenance Diet." The "Prudent Reducing Diet" is, in general, the "Prudent Diet" pattern without the vegetable oils and recommended margarines permitted those persons without a weight problem. This gives a P/S ratio of about 0.75.

To this basic pattern sufficient bread, cereals, fruit, and vegetables are added to make up the desired caloric level, usually about 1,600 for men and 1,200 for women. When weight reduction is completed, the vegetable oil and recommended margarine allotments

are added and the amount of bread, cereals, fruits, and vegetables are adjusted so that the "Prudent Reducing Diet" is now converted to the "Prudent Maintenance Diet."

The effects of these reducing diet patterns on serum cholesterol levels have been described.[9, 10] Of a starting group of 211 men, 50 to 59 years old, 111 (52.6 per cent) adhered so rigidly to the prescribed reducing diet as to achieve a Performance Index[11] of 85 or better during the first 10 weeks of observation. Their average control serum cholesterol dropped from 261 to 225 mg. per cent by the end of 6 weeks (fig. 2) and remained level thereafter ($t = 6.78$, highly significant). Of the 111 men, 97 reduced to desirable levels, 75 of these have been maintained on the "Prudent Maintenance Diet" for at least 6 months, and 56 of these maintained for at least 1 year with the average serum cholesterol remaining level.

Therefore, with respect to effect on serum cholesterol, strict adherence to the "Prudent Reducing Diet" yields results similar to those obtained by the use of the "Prudent Diet" with normal weight men. Further, maintenance of weight after successful weight reduction by use of the "Prudent Maintenance Diet" serves to maintain the lowered serum cholesterol level and prevents the rebound experienced by the more usual type of reducing and maintenance diets.[10]

When the subjects are divided into tertiles, the results are similar to those obtained by use of the "Prudent Diet" among men of normal weight. In the highest third, the average of 307 mg. per cent fell to 254 mg. per cent; 251 mg. per cent in the middle third fell to 222 mg. per cent; 207 mg. per cent in the lowest third fell to 198 mg. per cent. The lower limit reached by each tertile corresponds very closely to its counterpart in the men of normal weight. The major point of difference lies in the time necessary to achieve the low value—6 weeks on the reducing diet as compared to 5 to 6 months on the prudent diet.

Therapeutic Diet Pattern

A "Therapeutic or Vegetable Oil Diet" pattern becomes important whenever the "Prudent Diet" pattern fails to lower the serum cholesterol and other serum lipid fractions to desirable levels.

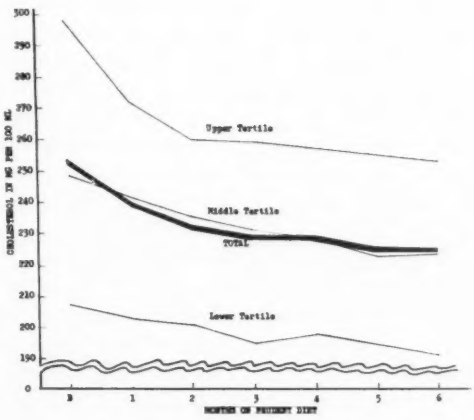

Figure 2

One-hundred eleven obese men, 50 to 59 years old, on prudent reducing diet to 10 weeks. Total and tertiles.

It is advisable to start immediately on the "Therapeutic Vegetable Oil Diet" pattern if the subject has essential hypercholesteremia or exhibits xanthelasma, xanthoma tendinosum, or a serum cholesterol level above 400 mg. per cent.

The "Therapeutic Vegetable Oil Diet" patterns devised by Kinsell et al.,[12] Brown and Page,[13] and Ahrens et al.[14] are all based upon the common principle of reducing to the barest minimum the amount of saturated fatty acids derived from ruminant animal flesh, dairy products, egg yolks, and all types of hydrogenated margarines and shortenings. In addition, 2 to 4 ounces (60 to 120 Gm.) of a vegetable oil rich in polyunsaturated fatty acids, such as corn, cottonseed, safflower, soybean, and sunflower, are added daily. Protein sources are primarily non-fat milk, skim-milk cottage cheese, selected nuts, egg whites, fish, and seafood. The more liberal of these diets may contain small amounts of chicken or turkey, while the ruminant animal meats are limited to such special occasions as Christmas and anniversaries. Unlike the "Prudent Diet" pattern, these diets, in our opinion, are dras-

tic and should be used only under medical supervision. A polyvitamin capsule containing supplementary amounts of all the essential vitamins and iron should be routinely employed, since the "Therapeutic Diet" pattern, like many other diets where more than 25 per cent of the calories are derived from one food, is likely to be low in an essential micronutrient.

Tables that list the fatty acid composition of common dietary fats in terms of saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids per 100 Gm. have been published[15] and are useful for physicians or clinics who wish to offer a wide menu range. It is usually preferred, in those subjects in whom a "Therapeutic Diet" pattern is indicated, to start with the high ratios and liberalize to lower ones as clinical and laboratory progress occurs.

Ordinarily, for different calorie levels, do not change the basic diet pattern, but make the changes only in the amounts of bread, cereals, vegetables, and fruits. To insure sufficient amounts of vegetable oil, it is even more important than in the "Prudent Diet" to incorporate the oil in cooking, in salad dressings, emulsified in skim milk, and added to vegetables and cereals.*

In the high ratio diets, the use of walnuts is very important, as this food supplies large amounts of polyunsaturated fatty acids, chiefly linoleic, and provides a P/S ratio of 8.75. The limited supply of this food, however, has made us restrict its routine use to diets with P/S ratios of 2.5 to 3.0 or higher. For example, the daily inclusion of 2 ounces of walnuts in our 2.5 to 3.0 diet, with a cut of about 400 calories in bread, fruits, and vegetables is sufficient to raise the P/S ratio to about 3.0 to 3.5. The measured amount of walnuts, when used, can be used at the table, combined in salads, or on protein dishes, or used as snacks.

Menu plans for the "Therapeutic Vegetable Oil Diet" pattern at 2.5 to 3.0 and 4.0 to 5.0 P/S ratio, each at two calorie levels are available in recipes given by the New York City Department of Health.

*Recipes using vegetable oils in cooking may be obtained from the New York City Department of Health. Most of these recipes may be found in Appendix D of the second edition of "Clinical Nutrition."[15]

Low-Fat Diets

Low-fat diets are occasionally indicated rather than the "Prudent" or "Therapeutic" patterns. The chief indication for the use of low-fat diets to control serum lipid levels are found among a few hyperglyceridemic-hypercholesteremic patients as defined by Brown and Page.[16] These investigators report that two of nine such patients responded by an increase in serum triglyceride and cholesterol levels when placed on their vegetable oil diet pattern. The determination of serum triglycerides, however, is difficult and is not available in most hospitals or clinical laboratories. We recommend, in the absence of such facilities, that this type of diet be used in the relatively rare instances when the "Prudent" or "Therapeutic" type of diet elevates the serum cholesterol.

A qualitative low-fat diet that will meet most purposes can be adapted from the "Prudent Maintenance Diet" pattern by the simple omission of the vegetable oil and recommended margarine and the isocaloric substitution of fruits, vegetables, bread, and cereals. The low-fat diets so constructed will yield 10 to 12 per cent of total calories as fat. At the 2,300-calorie level, it will provide 20 to 30 Gm. of fat and 15 Gm. at the 1,800-calorie level, each with a P/S ratio of about 0.75.

Another method is to use the low-fat menus provided by Keys and Keys.[17]

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We have seen that there is no absolute truth apart from mathematical principles; in all natural phenomena the principles from which we start, like the conclusions which we reach, embody only relative truths. The experimenter's stumbling block, then, consists in thinking that he knows what he does not know, and in taking for absolute, truths that are only relative. Hence, the unique and fundamental rule of scientific investigation is reduced to doubt, as great philosophers, moreover, have already proclaimed.—CLAUDE BERNARD. *An Introduction to the Study of Experimental Medicine.* New York, The MacMillan Company, 1927, p. 49.

CLINICAL PROGRESS

Clinical Interpretation of the One-Stage Prothrombin Time

By ARMAND J. QUICK, PH.D., M.D.

History

BIRTH of the idea of the one-stage prothrombin time test came with the speed of thought—its development, perfection, and full appraisal have not been entirely completed in a quarter of a century.[1] Its initial success is attributable to the fortuitious discovery of an active thromboplastic material. Rabbit lung was the first tissue tested and while it was found moderately satisfactory, it was soon replaced by rabbit brain. The latter material could readily be made almost bloodless merely by mechanically removing the pia and the larger blood vessels. In the earlier studies, air-dried rabbit brain was used. It had, however, the disadvantages of not having a uniform potency and being difficult to preserve. By a simple process of dehydrating the rabbit brain with acetone, a product was obtained with a high and constant potency and a remarkable stability. A preparation made and sealed in vacuum in April 1938 still gave 12 seconds on human plasma in a recent test as it had 22 years ago. Since this product gives very prolonged prothrombin times on plasmas from patients with severe hypoprothrombinemia[2] and with deficiencies of factors V,[3] VII,[4] and X[4] (Stuart-Prower defect), it is clear that it is devoid of any of these factors. This reagent fulfills the necessary requirements, for as Koppel et al.[5] stated: "The ideal thromboplastin, then, for use in the control of anticoagulant therapy should have reasonable stability, uniform reactivity both from lot to lot and year to year, and be one which is free of any of the known factors influenced by anticoagulant drugs."

Modifications

The test has met the requirements for the control of oral anticoagulant therapy and has served as a useful procedure in research. Yet, it has been repeatedly modified, and because of that, its wide adoption as a standard procedure has been stymied. In order to learn why the method has been modified, it seems desirable to consider a few of the most common procedures that differ in various aspects from the original method.

One of the first modifications was that of Campbell, Smith, Roberts, and Link[6] in 1941. Their modification deviated very little from the original test except that they reverted to the use of air-dried rabbit brain, which had already been replaced by the acetone-dehydrated product. The other changes were minor. Instead of adding thromboplastin and calcium separately, they combined them, and performed the test on plasma diluted 1 to 8 with saline. Instead of increasing the sensitivity of the method, they actually decreased it because their thromboplastin is less potent, and at high dilution, the reduced concentration of fibrinogen exerts a slowing effect on the prothrombin time.

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The Shapiro modification[7] likewise is not a true modification but actually is a reversion, because the most important detail of his method is the employment of desiccated rabbit lung, which was the material used first in the development of the test. It was abandoned because of the difficulty of removing blood. It is now known that blood as an impurity contaminates the preparation with serum factors, particularly VII. As a result of this, the test loses its sensitivity to factor VII. Since this is the factor that is mainly affected by Dicumarol, the modification is definitely less satisfactory than the unmodified procedure with acetone-dehydrated rabbit brain as the thromboplastin reagent. As a matter of fact, in many studies in which the Link-Shapiro modification is used, acetone-dehydrated rabbit brain replaces the reagents advocated by these authors. The actual difference between the modification and the original test is in the dilution of the plasma with saline and in the determination of the clot by means of a wire loop. As already stated, dilution of plasma increases neither the sensitivity nor the accuracy of the prothrombin time. As to timing the formation of the clot, the original technic of gently tilting the tube and watching for the incipient appearance of the fibrin web is exceedingly accurate and reproducible to a fraction of a second. If an operator can obtain exactly the same prothrombin time with the wire-loop technic as with the tilting procedure, it is immaterial which way he chooses to time the clot. It is doubtful, however, whether any superimposed mechanical means to time clotting can improve on the accuracy of the visual tilting technic.

The most unfortunate modification of the one-stage test was the substitution of Russell's viper venom for rabbit brain.[8-10] This agent as a thromboplastin is insensitive to changes in factor VII and, therefore, fails to record accurately the reduction of prothrombin activity of coumarin and indanedione drugs, which depress mainly factor VII. Although in early studies with this agent, such as those of Prandoni and Wright,[11] a surprisingly high percentage of hemorrhages occurred in patients treated with Dicumarol, it was not until Wilson[12] pointed out that Russell's viper venom gave unreliable results that the reagent was gradually abandoned.

Interestingly, the clotting time has been proposed to replace the prothrombin time[13, 14] and surprisingly good results with it to control anticoagulant therapy have been reported.[15] This is difficult to explain because a depression of factor VII has no effect on the clotting time. Lempert[16] has pointed out that the clotting time does not appear to give sufficient warning of dangerously low prothrombin times, and that it is likely that the prothrombin time carried out with Russell's viper venom also often gives misleading results that lead to overdosage of Dicumarol. Both vitamin K deficiency and Dicumarol depress factor VII. This is not recorded by the clotting time but it nevertheless decreases hemostatic efficiency. The incidence of bleeding is lower than one would expect when tests insensitive to a low factor VII concentration are employed. This can be explained by the wide margin of safety in the prothrombin activity of man. As pointed out many years ago,[17] the concentration can be reduced to about 20 per cent of normal before a serious hemorrhagic state develops. A distinction must be drawn between a potential bleeding tendency and actual bleeding. Thus, as has been shown dramatically, a rabbit with a prothrombin time prolonged to 25 seconds by Dicumarol does not bleed spontaneously but invariably dies from hemopericardium following a heart puncture.[18] A patient may have an alarming depression of prothrombin activity as measured by the unmodified one-stage test, yet may fail to bleed until a superimposed factor such as trauma comes into play.

The series of modifications of the one-stage prothrombin time developed by Owren deserve particular attention because of their wide clinical acceptance. In 1948 he[19] described his first modification, which consisted merely in diluting plasma and mixing the diluted plasma with ox plasma adsorbed with asbestos. Brain thromboplastin and calcium were added to this mixture in a manner similar to the

original one-stage test. Claims for the need of the modification were that the original one-stage test showed no significant prolongation of the clotting time until the concentration of prothrombin drops below 50 per cent of normal and that the concentration of factor V is a variable that must be made constant. Neither of these two claims is well founded. In the hands of even a moderately skilled investigator, a change in the prothrombin time of a half second can readily be determined. A decrease of 50 per cent activity increases the prothrombin time from the normal of 12 seconds to 15, which is a significant increment of 3 seconds. In the control of anticoagulant therapy, it is usually the aim to double the prothrombin time and the desired value of 24 to 26 seconds can easily be timed. In regard to factor V, it is established that normal plasma contains an excess of this agent and that 50 per cent can be lost before the prothrombin time is effected. Furthermore, factor V is not reduced by Dicumarol; therefore, no need actually exists to supply extra amounts from outside sources.

Special caution must be exercised in accepting the results obtained with adsorbed plasma as a diluting plasma. It is to be remembered that Bordet and Delange[20] originally considered plasma treated with $Ca_3(PO_4)_2$ as essentially a solution of fibrinogen devoid of other clotting factors, which Nolf[21] justifiably challenged. In 1943 it[22] was shown that the newly discovered clotting factor (labile factor) was not adsorbed by $BaSO_4$ or $Ca_3(PO_4)_2$. Later, it was found that another factor that appears to fix the prothrombin time in human plasma and that has been designated as the prothrombin time fixing agent (PTFA)[23, 24] also is not removed by $Ca_3(PO_4)_2$. The probability that additional factors that may perhaps be accelerators or inhibitors remain in adsorbed plasma cannot be ignored. This further complicates the problem because bovine plasma differs distinctly from human plasma. Obviously, the interpretation of the results obtained either with Owren's first modification or with the second, namely, the P and P test,[25] is difficult. It should be emphasized that a comparison of the original one-stage method with these two tests, which are based on empirical dilutions employing nonhuman plasma, cannot be done successfully on a theoretical basis. Clinically, the two modified tests have apparently been superseded by a new procedure, the thrombotest.[26]

This procedure is a one-stage test in which an all-in-one reagent is added to citrated plasma. This reagent is a mixture of a crude ether extract of either human brain or soya bean, adsorbed bovine plasma, ox or horse brain, and calcium chloride. The preparation of these materials and the proportion in which they are mixed is not given in sufficient detail to make it possible to carry out the preparation one's self. This necessitates dependence on a commercial source. A comparison of such a complex empirical method with the simple original one-stage test is beset with difficulties both theoretical and practical. When the thrombotest is compared clinically with the so-called Quick test, the precise directions of the originator's procedure should be followed and not one of the numerous modifications.

Interpretation of the One-Stage Test

In fresh normal human plasma, the prothrombin time is fixed by the free or active prothrombin[23] which seems to be one of the most constant constituents of human blood. Contrary to the statement of Biggs and Douglas[27] that the one-stage test is relatively insensitive to changes of prothrombin, the very opposite is true. Any change in the concentration of free prothrombin is readily detectable and can be determined quantitatively. Factors V, VII, and X (Stuart-Prower), on the other hand, must be greatly reduced before the change is detectable by the basic prothrombin time test. Thus, the concentration of factor V must be decreased over 50 per cent before the prothrombin time is prolonged.[28] The normal value of 12 seconds furnishes no assurance that factors V, VII, or X are entirely normal in concentration but is proof that the free prothrombin is not reduced. A prolonged prothrombin time, on the contrary, indicates that any one or more of the factors that constitute the prothrombin complex may be low. The one that is reduced most becomes the determinant of the prothrombin time.

Prothrombin and the ancillary factors act independently of one another and a deficiency of one is not compensated by an excess of another. Thus, a low concentration of prothrombin or of factor VII is not influenced, as measured by the prothrombin time, by an excess of factor V no matter how great it might be (table 1). When more than one factor is decreased, the effect is not additive. For instance, in Dicumarol therapy both factor VII and prothrombin are decreased, but because the first is reduced more quickly and to a much greater degree, the prothrombin time is actually determined by the concentration of factor VII (table 2) and could rightly be called the factor VII time. Since in other conditions, the prothrombin time may measure another constituent of the complex, the best name for the basic test is prothrombin activity time, or merely prothrombin time, with the understanding that the term prothrombin in this instance refers to an activity and not to the specific compound.

Table 1

Effect of Excess Factor V on the Prothrombin Time in Hypoprothrombinemic States

Volume of adsorbed rabbit plasma* ml.	Prothrombin Time Deficiency of			
	Normal sec.	Factor V sec.	Factor VII sec.	Prothrombin sec.
0	12	50	41	20
0.01	12	12	40	20
0.02	12	12	40	20
0.05	11.5	11.5		20

*As a source of factor V added to 0.1 ml. of plasma tested.

Adaptation of the One-Stage Test for the Determination of Specific Factors

Factor V. To determine whether a prolonged prothrombin time is due to a decrease of factor V, the oxalated plasma to be tested is mixed with an equal volume of fresh normal oxalated human plasma adsorbed with $Ca_3(PO_4)_2$. If the prothrombin time of the mixture is normal, it can be concluded that the patient's plasma lacks factor V. The correction effected by the normal adsorbed plasma is brought about by a restoration of an adequate level of factor V. The exact concentration can be determined by the assay method recently outlined.[27]

Factor VII and Prothrombin. Aged serum from normal blood is devoid of factor V, very low in prothrombin, but rich in factor VII. By adding 1 volume of aged serum to 9 volumes of the plasma to be tested, the prothrombin time is completely normalized if the deficiency is due solely to factor VII but is not corrected if the defect is pure hypoprothrombinemia, and is only partially rectified when both factors VII and prothrombin are depleted, as occurs in Dicumarol therapy (table 2). Factor X (Stuart-Prower) is not included in this discussion under factor VII. Too little is known about this agent to warrant attempting a separate quantitative estimation.

The One-Stage Test in the Control of Oral Anticoagulant Therapy

It has been stated that "oral anticoagulant therapy is only as good as its laboratory control."[28] While this statement is quite true, the answer to what constitutes adequate laboratory control remains indefinite. Most workers agree that the one-stage prothrombin time is the sine qua non of laboratory control, but there seems to be no general agreement on how the test should be carried out. Modifications of the test have been indiscriminately accepted, often for no other reason than that they were considered to be simplifications of a simple test.

One of the most important requirements of the one-stage test is the use of a thromboplastin that is devoid of factor VII,[29] because it is this agent that is affected most by Dicumarol and its allied drugs. As already stated, acetone-dehydrated rabbit brain fully meets this requirement. Preparations of thromboplastin contaminated with serum, which are almost unavoidable when tissues are employed from which blood is difficult to remove, are likely to contain traces of factor VII and are therefore unsatisfactory.

In the routine control of Dicumarol, nearly every modification of the one-stage method, even when grossly defective on theoretical grounds, has generally been reported to be fairly satisfactory. This can be accounted for only by the wide margin of safety in pro-

Table 2

Determination of Prothrombin in Plasma by the One-Stage Method with Aged Normal Serum

Plasma	Prothrombin Time: Basic sec.	Corrected with aged serum sec.	Calculated prothrombin activity %	Calculated prothrombin concentration %
Normal	12	11-12	100	100
Congenital hypoprothrombinemia	22	22	25	25
Congenital factor VII deficiency	60	12	6	100
From patients on Dicumarol therapy	25	17	20	40
From patients on Dicumarol therapy	37	19	12.5	32
From patients on Dicumarol therapy	22	13.5	25	75

thrombin activity. Considering how badly the prothrombin time has occasionally been carried out, one must conclude that sometimes the test serves mainly to give moral support and, unfortunately, with the price of false security.

Since the reagents for a satisfactory one-stage test are easily prepared or obtainable commercially and, since the procedure is exceedingly simple, any laboratory should be able to obtain normal values of 12 seconds and a reproducibility within a half second. This will insure much greater safety. An accurate prothrombin time should be done on every patient prior to anticoagulant therapy. A deviation as small as 1 second should not be ignored and an effort should be made to find the possible cause. It may be due to liver dysfunction, faulty nutrition, effect of various drugs, or it may have genetic significance. Many individuals who are heterozygotes to a coagulation defect in the prothrombin complex have a slightly prolonged prothrombin time. These will invariably be missed if a modification of the test is employed that permits a normal range of several seconds.

To obtain an accurate prothrombin time, the test should be carried out within 2 hours after the blood is collected. In the usual hospital routine, this is generally done or can be arranged if the importance of promptness is recognized. When blood stands several hours, various changes slowly take place. One is a gradual loss of factor V. This can be minimized by keeping the blood cold, which is easily accomplished by putting the test tubes in a beaker filled with chipped ice. At room temperature, other changes occur that prolong the prothrombin time and these are irreversible. At 37 C. this deterioration is fairly rapid.

When oxalated or citrated blood is exposed to glass surface, an activation results that has been interpreted as a conversion of inactive prothrombin to the active state. Because factor V is lost simultaneously, the activation is masked. In a silicone-coated container, activation is practically absent. Thus, after restoration of factor V, which can easily be done by adding deprothrombinized rabbit plasma, the prothrombin time of the plasma stored in glass for 24 hours or more becomes 8 seconds whereas that in silicone becomes 12 seconds, which is the original value of fresh plasma.

On the basis of these observations, conditions can be devised for obtaining reliable prothrombin times on stored blood. The oxalated blood or plasma is transferred to a silicone-coated test tube, which is kept at 4 C. Before the prothrombin time is done, the lost factor V is replaced. The most suitable agent for this is deprothrombinized rabbit plasma. In practice, 0.01 ml. of the latter is mixed with 0.09 ml. of the plasma before the thromboplastin and calcium are added (table 3).

The loss of labile factor is much slower when 0.1M sodium citrate is used instead of 0.1M sodium oxalate as the anticoagulant, and therefore the prothrombin time is less affected, as Neilson and Briggs[30] have observed. The other less defined change that

occurs at room temperature and much more at 37 C. brings about an irreversibly prolonged prothrombin time in both citrated and oxalated plasmas. This precludes sending specimens for prothrombin determinations by ordinary mail.

For the ordinary routine, when the test is carried out promptly, the use of ordinary glass test tubes is satisfactory. When research accuracy is desirable, the blood should be kept in silicone-coated tubes, especially when the determination has to be delayed. In this way, activations such as Winterstein and Studer[31] have again recently observed are obviated.

Studies on oral anticoagulant therapy have followed a rather set pattern. The drug is given in such dosage that the prothrombin time is elevated until it reaches empirically fixed limits. In many studies, the aim is to increase the prothrombin time to twice normal. In reports of the clinical results, which usually include untoward effects such as hemorrhage, often little information is given on how the prothrombin time was performed. Not infrequently, one finds statements such as "control of dosage, judged, as is usual, by the Quick one-stage prothrombin time."[32] Yet, on inspecting the results, one finds that the test as carried out had little resemblance to the technic recommended by the author.

The need for a standardized prothrombin time test is clearly recognized and eventually the goal will be achieved. Even now, with the various modifications of the method for control, serious bleeding in long-term oral anticoagulant therapy is fairly uncommon. Perhaps a thorough study of the relationship of the decrease of factor VII to that of prothrombin might furnish valuable information. By a simple additional step in the prothrombin time test, i.e., adding stored normal serum to the plasma, both the prothrombin and factor VII can be quantitatively estimated. The possibility is thus offered that such data could be used to reevaluate the therapeutic range to be attained to make therapy both safer and more effective.

In long-term anticoagulant therapy when the prothrombin activity level is greatly depressed, an apparent decrease of factor IX (PTC) occurs. Since this agent is present in the blood in an inactive state, it is difficult to determine quantitatively. Faulty activation of factor IX can easily be mistaken for a true deficiency. Since it has been found by one of my associates that a depression of factor IX activity only appears when factors VII and prothrombin are markedly reduced, a quantitative determination of the latter two factors suffices for adequate clinical control of oral anticoagulant therapy.

Table 3

Prothrombin Time of Plasma from Normal Subjects and from Patients Receiving Dicumarol. Effect of Storage

Plasma	Prothrombin Time, Fresh sec.	Stored for 24 hours at 4 C.* Uncorrected sec.	Stored for 24 hours at 4 C.* Corrected for factor V sec.
Normal	12	15	12
Normal	12	16	12
Dicumarol	25	35	24
Dicumarol	37	47	39
Dicumarol	32	45	28

*In silicone-coated tubes.

Conclusion

In the original one-stage prothrombin time test, sodium oxalate is the anticoagulant and an extract of acetone-dehydrated rabbit brain is the thromboplastin reagent. A clotting time of 12 seconds on normal adult human plasma is consistently obtained.

On storage in glass, adult oxalated plasma loses factor V, which causes a prolonged prothrombin time. Simultaneously, an activation occurs that is masked, but on restoration of the lost factor V, a reduction of the prothrombin time to 8 seconds is observed. In a silicone-coated container the loss of factor V occurs but the activation is greatly delayed; therefore, the prothrombin time is corrected to 12 seconds by excess factor V.

A prolonged prothrombin time may occur from a deficiency of prothrombin, factors V, VII, and X (Stuart-Prower). The effect when more than one of these factors is reduced is not additive nor does an excess of one compensate for a decrease of another.

Aged normal serum, which is rich in fac-

tors VII and X (Stuart-Prower), and deprothrombinized (adsorbed) rabbit plasma, which has an exceptionally high concentration of factor V, serve as valuable reagents that can be employed to make the basic prothrombin time a specific procedure for the quantitative determination of each major agent of the prothrombin complex.

A few of the numerous modifications of the one-stage method are discussed.

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ABSTRACTS

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Nairn, R. C., Chadwick, C. S., and Fraser, K. B.: Purification of Renin by Electrophoresis, Adsorption and Immunological Methods. Brit. J. Exper. Path. 41: 214 (June), 1960.

Renin was initially purified from pig kidneys by the fractional method of Haas et al. as far as step 6; it was further purified by electrophoresis in starch gel, kaolin adsorption and immunologic precipitation of impurities by specific antisera. The antisera prepared in rabbits against homogenate of pig kidney cortex or in hens against step-6 renin, produced precipitins against pig kidney protein impurities. The antisera were used for immunologic analysis by gel diffusion. The purest renin sample was obtained by electrophoresis; immunologically pure preparations were obtained by removal of the precipitinogens by the antisera; however, these preparations were less pure chemically due to contamination by the rabbit or hen serum proteins. The contamination was reduced by the kaolin adsorption method. The gel diffusion method provides a simple and economical method of testing the purity of renin preparations.

KALMANSOHN

RHEUMATIC FEVER

Johnson, E. E., Stollerman, G. H., Grossman, B. J., and McCulloch, H.: Streptococcal Infections in Adolescents and Adults after Prolonged Freedom from Rheumatic Fever. I. Results of the First Three Years of the Study. New England J. Med. 263: 105 (July 21) 1960.

Two hundred and ninety-eight adolescents and adults with previous rheumatic fever, but who had been free of rheumatic fever for at least 5 years, were observed in regard to the incidence and complications of streptococcal infections in the absence of antistreptococcal prophylaxis. In this group appropriate antibiotic therapy was instituted only when clinically apparent, symtomatic streptococcal infection developed. Routinely two monthly throat cultures and serum streptococcal antibody determinations were employed to detect asymptomatic infections. In the adolescents (ages 11 to 22 years) the rate of streptococcal infection was 23.2 per cent per patient year and in the adults (ages 23 to 70 years) 12.8 per cent. Recurrences of rheumatic fever occurred in seven patients in the adolescent group—a rheumatic fever recurrence rate of 1.8 per cent per patient year and 9 per cent subclinical streptococcal infection. No rheumatic fever recurrences were found in the adult patients in this study. When these figures were contrasted with those of concomitant studies in children receiving prophylaxis (recurrence rates of 2.4 per cent per patient year and 17.5 per cent per subclinical infection), it is evident that there is a downward trend with age in the incidence of streptococcal infections and in the frequency with which these infections reactivate rheumatic fever. However, the authors emphasized that these preliminary data should not be construed as a sound basis for modifying current recommendations concerning the duration for which antistreptococcal prophylaxis should be maintained in the rheumatic subject.

SAGALL

Soloff, L. A.: The Failing Rheumatic Heart Mechanisms and Present Day Therapy. Am. J. M. Sc. 240: 1 (July), 1960.

The author's current approach to acute rheumatic fever and its complications and his indications for special investigations and surgical attack in chronic rheumatic heart disease are described in detail. The clinical course of the various valvular lesions is discussed in detail and illustrative cases are outlined. It is emphasized that the expectation of life in rheumatic valvular disease has increased over the past 30 years because of improvement in prophylaxis and in drug therapy. In addition, emphasis is placed on the concept that congestive heart failure in subjects with rheumatic heart disease is a combination of myocardial, valvular, and pulmonary defects and associated illnesses. The ability of the surgeon is still inadequate to cope with combined valvular lesions of the aortic and mitral valves. For these reasons the author's indications for valvular surgery at this time are based upon clinical disability, explained by hypertension attributable to distal valvular dysfunction.

SHEPS

Streitfeld, M. M., and Saslaw, M. S.: Beta Hemolytic Streptococci and Rheumatic Fever in Miami, Florida. II. Antistreptolysin O Titer Determinations between October 1954 and May 1955. Dis. Chest 37: 211 (Feb.), 1960.

Antistreptolysin-O (ASLO) titers of blood drawn from 333 children attending the first three grades of public schools in Miami, Florida, were determined in conjunction with studies of beta-hemolytic streptococci isolated from the throats of the same subjects. ASLO levels were lowest in the bloods of those children from whose throats no streptococci or only group B organisms were isolated; next higher with groups F and G; still higher with group C, and highest with group-A organisms. Serial ASLO titers showed a rise in children from whose throats group-A beta-hemolytic streptococci were isolated. A similar but lesser rise was demonstrated in children with group-C throat cultures. Children without beta-hemolytic streptococci cultures showed a negligible rise. High-colony counts on original isolation plates were more likely to be associated with a two-tube or greater ASLO-titer elevation than were low-colony counts.

MAXWELL

ROENTGENOLOGY

Baker, H. L., Jr.: A New Approach to Percutaneous Subclavian Angiography. Proc. Staff Meet., Mayo Clin. 35: 169 (Mar. 30), 1960.

To prevent pneumothorax caused by other technics the authors describe their method of percutaneous subclavian angiography. A needle is directed through the skin in the supraclavicular region toward, and finally into, the subclavian artery and, when this is accomplished, 10 ml. of a 50 per cent solution of diatrizoate (Hypaque) is rapidly injected and several films are obtained. This series of films with a right-sided injection will show the condition of the innominate, carotid, subclavian, and vertebral arteries in the neck, and will show the condition of the latter two vessels with injection on the left. Lateral exposures are used to demonstrate the carotid bifurcation as well as the vertebral, basilar, and intracranial system of arteries.

KRAUSE

Bartley, O.: Electrokymographic Changes in Myocardial Infarction. Acta radiol. 54: 81 (Aug.), 1960.

Thirty-six patients with myocardial infarction were studied with electrokymograms at periods of from several weeks to several years after the onset of symptoms. Completely paradoxical ventricular movements during systole indicative of ventricular aneurysm were observed in seven patients. A partially paradoxical systolic movement was observed in 19 patients. Uncertain ventricular changes were noted in eight patients, but no changes were noted in two patients. Eighty per cent of the patients showed evidence of obstructed flow from the left atrium. The completely paradoxical ventricular curves during systole were thought to be due to a severely damaged muscular wall. The less marked paradoxical movement during the initial ejection phase was the most commonly observed abnormality but was not considered pathognomonic of myocardial infarction. The changes in the atrial curves were thought to be due to an intra-atrial conduction disturbance with dilatation and hypertrophy or atrial infarction.

KALMANSOHN

Begg, A. C.: Some Radiological Aspects of Ischemia of the Brain. Brit. J. Radiol. 33: 311 (May), 1960.

When an obstructive lesion affects the arteries supplying the brain proximal to the circle of Willis, the clinical diagnosis becomes more difficult as the area of brain involved is more diffuse. The more proximal the arterial obstruction, the milder and more vague are the symptoms. Recently, effective medical and surgical treatment has made the diagnosis and localization of these lesions important. Most of the radiologic

information is obtained by arteriography. The left vertebral system is best visualized by catheterizing the subclavian artery through the brachial artery. Injection is made against the blood stream increasing the concentration of contrast material and avoiding trauma to the vertebral artery itself. On the right side, injection after catheterization of the brachial artery with the tip of the catheter in the subclavian artery (or in the innominate artery if simultaneous carotid arteriogram is desired) will produce good pictures. The carotid system can be visualized by percutaneous arteriography. However, trauma to the vessels is a hazard, and the proximal portions of the artery may not be visualized. Catheterization of the innominate artery via the right brachial artery and of the left common carotid by way of either femoral artery is preferable. This is so because there is less trauma to the vessels supplying the brain, and less concentration of contrast material in the brain. Also, evaluation of the part played by each vessel is possible, the examination is more comfortable for the patient, and better radiation protection is possible for the staff. Cases are presented where no accurate estimate of the situation was possible without arteriography of the components feeding into the circle of Willis. This could be readily and safely demonstrated by the methods described and the information determined the type of treatment needed.

KITCHELL

Bjork, V. O., and Lodin, H.: The Evaluation of Mitral Stenosis with Selective Left Ventricular Angiocardiography. J. Thoracic Surg. 40: 17 (July), 1960.

The authors have employed left ventricular angiocardiography for the evaluation of the stenotic component in mitral valvular disease. In this particular report, they employed a method with the patient in the supine position in which a needle was introduced through the apex beat and directed toward the right second costochondral junction under local anesthesia. They demonstrated a characteristic dome formation in patients with mitral stenosis. This particular formation is due to the fused mitral valves forming a dome during diastole. This dome bulges into the left ventricle, making a sharply outlined filling defect in this chamber. It can be seen in both the frontal and lateral projections. Mitral stenosis was found at operation in all 20 patients in whom a dome had been found preoperatively in the left ventricular angiocardiogram. The stenosis was severe in all but one patient in whom it was very mild, admitting 1½ fingers. No dome formation was found in patients in whom there was no mitral stenosis. Occasionally a false dome formation was observed in the lateral projection. In these patients, the atrial wall simulated a dome caused by fused mitral valves but this could not be observed in the anteroposterior projection. Furthermore, this false dome in the lateral projection persisted during systole, which, of course, did not occur with a true mitral stenosis. Usually this dome defect appeared rounded but owing to the relation between an eccentric orifice and the projection used the defect appeared more slitlike and the border of the anterior leaflet was sometimes seen below that of the posterior leaflet. The absence of a dome in the anterior projection in patients with an enlarged left ventricle cannot exclude the presence of mitral stenosis, since excessive contrast media in the left ventricle will mask the dome.

LEVINSON

Bolt, W., and Rink, H.: The Terminal Pulmonary Blood Vessels in Normal and Pathologic Angiograms. Fortschr. Röntgenstr. 93: 21 (July), 1960.

From examination of numerous selective pulmonary angiograms it was concluded that the lobular artery is an end artery and shows no anastomoses, while the lobular veins show numerous anastomoses with neighboring lobular veins. Anastomoses between pulmonary and bronchial arteries could not be demonstrated in normal lobuli but might appear in parenchymal sclerosis. Arteriovenous anastomoses could not be found under any circumstances. The control mechanism for the circulating blood volume seemed to be situated primarily in the capillary portion of the pulmonary circulation, but in pathologic cases it became displaced toward the arterial limb because of reduction of the capillary bed. Parenchymal atrophy caused an increase in the lobular volume, rarefaction of the vascular net, and stenosis of the arterial limb. Parenchymal sclerosis led to decrease of lobular volume, stenosis of the capillary and postcapillary limbs, and formation of arterio-arterial anastomoses. Localized lobar destruction of parenchyma at first decreased the number of blood vessels and then caused the formation of blind ends of the lobular arteries, while the venous limb could no longer be demonstrated.

LEPESCHKIN

Di Guglielmo, L., Baldrighi, V., Montemartini, C., and Schifino A.: Roentgen Investigation of the Coronary Veins in the Dog. Acta radiol. 53: 191 (Mar.) 1960.

Thoracic aortographies were performed in 73 living dogs. When correctly performed, there was satisfactory filling of the coronary arteries in all examinations. In 37 of 223 aortographies, films were obtained which identified the coronary venous circulation. The contrast filling of the veins was thought to be related to the degree of filling of the coronary arteries, as evidenced by the fact that the phlebographic stage was constantly reached when a high concentration of contrast medium had been obtained in the coronary arteries. However, good demonstration of the coronary arteries was not always accompanied by the appearance of the venous elements. After the intravenous administration of epinephrine-type substances, contrast filling of the coronary veins was more frequent and more dense.

KALMANSOHN

Dotter, C. T.: Left Ventricular and Systemic Arterial Catheterization: A Simple Percutaneous Method Using a Spring Guide. Am. J. Roentgenol. **83:** 969 (June), 1960.

Percutaneous, spring-guided catheterization of the left ventricle, the aorta, and systemic arteries is a reasonably safe, simple, and effective procedure for obtaining detailed anatomic and physiologic information. It is easily carried out on unanesthetized outpatients. A detailed description of this method is given. The percutaneous retrograde femoral-aortic approach is useful not only in diagnostic visualization but also as a means for obtaining hemodynamic data and a route for selective drug administration.

KITCHELL

Gebhardt, W., Danner, D., Reindell, H., and König, K.: Report of a Study Comparing Two Roentgenographic Methods of Determining Heart Volume. Acta med. scandinav. **167:** 467, 1960.

In a series of paraffin heart models the tomographic method described by Gebhardt was shown to be the most accurate one. It was therefore applied in 25 cardiac patients and 25 normal healthy persons to evaluate the degree of exactness of the Rohrer-Kahlstorf technic, modifications of which are the most commonly used roentgenologic methods for determination of the heart volume. Deviation of values obtained by this technic from actual heart volume was found to be slightly higher than in the Gebhardt method and in the majority of subjects the Rohrer-Kahlstorf method of measurement furnished values that were somewhat lower.

SHEPS

Greenspan, R. H., Bernstein, E. F., and Loken, M. K.: Intravenous Aortography: Technique and Clinical Aspects. Am. J. Roentgenol. **83:** 1034 (June), 1960.

A safe and simple technic for performing aortography by means of the venous route is presented. It avoids the complications of translumbar aortography secondary to direct puncture of the aorta. In 204 aortograms made on 184 patients, there was no death or serious complication, and diagnostic information was obtained in over 90 per cent of the cases. After inserting a polyethylene catheter under local anesthesia into the median antecubital vein and properly positioning it, circulation time is accurately determined by injection of I^{131}-labelled renografin. The timing of the circulation to the aorta is accurately determined by means of a collimated scintillation counter connected through a rate meter to an Esterline Angus recorder. Using this information, a solution of diatrizoate is injected into the catheter as rapidly as possible (by means of an Elema-Schonander hand injector). Following a pause, equal to the arm vein to aorta circulation time as determined previously, roentgenograms are obtained in one or two planes (the authors in most cases used the Schonander biplane apparatus taking roentgenograms at 1 per second for approximately 8 seconds). Although delineation of the smaller vessels is not as detailed here as in direct aortography, the major arteries are well visualized and changes in caliber of flow can be clearly seen.

KITCHELL

Haimovici, H., Shapiro, J. H., and Jacobson, H. G.: Serial Femoral Arteriography in Occlusive Disease; Clinical-Roentgenologic Considerations with a New Classification of Occlusive Patterns. Am. J. Roentgenol. **83:** 1042 (June), 1960.

Since the advent of arterial grafting for occlusive arterial disease femoral arteriography has acquired increased importance. Determination of the site and extent of segmental occlusion, the state of the distal arterial tree, and the degree of collateral circulation can be best obtained by serialographic studies. The authors report 102 consecutive femoral arteriograms on 91 patients. They described full-length multifilm visualization secured by an automatic long-segment serialograph. This machine contains six 14 by 36-inch cassettes that can be serially exposed at predetermined intervals as selected on an interval-timer control box. Occlusive disease in the femoral popliteal system is classified into nine arteriographic patterns. Importance of the

"run-off" in the selection of patients for arterial grafting is emphasized and a classification of collaterals into three groups according to occlusion patterns of the femoral-popliteal segment is given. Prognostic considerations based on arteriographic patterns and degree of collaterals are arrived at by correlating them with clinical findings. In most instances a good correlation existed between the clinical and the angiographic findings, attesting to the reliability of serial arteriography.

KITCHELL

Holesh, S.: Dissecting Aneurysm of the Aorta. Brit. J. Radiol. 33: 302 (May), 1960.

Until recently, dissecting aneurysm of the aorta was regarded as fatal and the occasional recovery found in the autopsy room was considered a medical curiosity. An increasing number of acute dissections is being treated surgically, and immediate diagnosis improves the poor prognosis. Operation should be performed within 48 hours and copies nature's method of healing by establishing re-entry of the dissected passage distally into the aorta. Reconstruction operation with graft can be performed but depends on the extent and location of the lesion. The radiologic findings are determined by the stage in which the examination is made. Shortly after the acute phase the superior mediastinum is widened and the heart is considerably enlarged. The mediastinal widening is probably due to dilatation of the aorta and extravasation of blood into the mediastinum. The cardiac enlargement may be due to rupture into the pericardium or acute cardiac dilatation. The patient's poor condition precludes tilting maneuvers so that it is difficult to tell whether increased cardiac size is the result of dilatation or hemopericardium. Left hemothorax often obscures the heart border. Where recovery takes place, the aortic knuckle becomes more clearly defined roentgenologically and may return to normal size, usually however at a higher level than before. Often the aorta remains widened and a double aortic knuckle is visible. The normal width of the aortic wall is 2 to 3 mm. and dissection is suggestive if the thickness of the wall approaches 1 cm. If it is 1 cm. or more, there is little doubt about the diagnosis. With a slow leak before acute dissection occurs, the obvious diagnostic sign is marked difference in caliber of the aorta before and after rupture. In chronic cases the radiologic appearances depend on the location and extent of the previous dissection. When previous pictures are available showing calcification in the knuckle, such calcification is an easy baseline from which to measure thickness of the artery wall. Often the dissection stops just above the hiatus and a posteroanterior film showing a sudden alteration in caliber at this point may be diagnostic. Angiocardiography is of great value in doubtful cases. The total number of angiograms and aortograms performed in cases of dissection is small but these will increase, since it has been established that diagnosis may be lifesaving with present surgical technics.

KITCHELL

Jorgens, J., Blan, N., and Wilcox, W. A.: The Cinefluorographic Detection and Recording of Calcifications Within the Heart: Results of 803 Examinations. Radiol. 74: 550 (Apr.), 1960.

Many different methods have been employed for demonstrating intracardiac calcifications including roentgenography, roentgenkymography, and planography. Each of these has limitations. Over a 2-year period, 803 cinefluorographic examinations of the heart were performed at Veterans Administration Hospital in Minneapolis. The technic of the examination consisting of six film sequences of the heart and great vessels is described. On the basis of these studies, the authors consider cinefluorography the method of choice for detecting and recording calcifications within the heart.

KITCHELL

Keats, T. E., Lodwick, G. S., and Koenig, G. F.: Some Aspects of Cine- and High Speed Serial Angiographic Techniques. Am. J. Roentgenol. 83: 1067 (June), 1960.

The availability of technics for cine roentgenographic and high-speed serialographic technics of roentgenologic examination, in the Department of Radiology of the University of Missouri, permitted the clarification of some of the problems relating to these two modalities. Three broad aspects of the problem (dosimetry, relative diagnostic effectiveness, and evaluation of the relative roentgen opacities of various concentrations of contrast media) were studied. There was little difference in the radiation dose to the skin with either method, although more skin was irradiated with serial angiocardiography. Simple protection measures will guard attendant personnel. In lesions where the dynamics of flow were important, cineangiocardiography possessed advantages. Tests indicated that the radiopacities of 50 per cent and 85 per cent Hypaque were quite similar and the advantages of additional opacity were offset to a great extent by the disadvantage of the inherent increased viscosity and toxicity.

KITCHELL

Kincaid, O. W.: X-ray Diagnosis of Congenital Heart Disease. J. A. M. A. 173: 648 (June 11), 1960.

In about 75 per cent of patients with congenital heart disease, the type of malformation can be accurately determined and operability predicated by correlation of the history, physical examination, electrocardiographic findings, and conventional roentgenographic and fluoroscopic findings. Special methods such as cardiac catheterizations and angiocardiography must be utilized in the remaining 25 per cent. Congenital anomalies can be broken down into four groups (based on the changes in the lesser circulation) and further subdivisions of these groups (based on certain other differentiating features) can be made and prove to be a great practical value in diagnosis. Although in most instances the x-ray findings alone are not unequivocally diagnostic of a specific cardiac anomaly, by use of the suggested approach and by correlation with the clinical findings in a given patient an accurate diagnosis can often be established. In many instances specialized procedures, including cardiac catheterization, angiocardiography, and thoracic aortography, must be used for precise diagnosis.

KITCHELL

Kincaid, O. W., Brandenburg, R. O., and Bernatz, P. E.: Angiography as a Guide to Mediastinal Exploration. J. A. M. A. 173: 613 (June 11), 1960.

Angiocardiography and thoracic aortography have been carried out at the Mayo Clinic on 200 patients having a variety of mediastinal lesions. These procedures were often the only accurate means of distinguishing vascular from nonvascular lesions without exploration. The results of the studies may determine the exact nature, extent, and probable resectability of lesions of the mediastinum. In contrast, fluoroscopy and other diagnostic technics were inaccurate in distinguishing vascular from certain nonvascular lesions. Twelve case histories are given to illustrate the value of information obtained by angiography. These showed the possibility of avoiding unnecessary and possibly hazardous mediastinal exploration in some patients; and in other cases indicated the necessity of surgical exploration. No fatalities and no serious reactions were encountered in the entire group of patients with either angiocardiography or thoracic aortography.

KITCHELL

Klatte, E. C., Campbell, J. A., and Lurie, P. R.: Aortic Configuration in Congenital Heart Disease. Radiology 74: 555 (Apr.), 1960.

In well over 600 angiocardiograms at Indiana University Medical Center over the past 12 years, the aortic configuration was found to be the key to the recognition and differentiation of many primary types of congenital and acquired cardiac lesions. By use of selective cinecardioangiography in the past 3 years, the importance of aortic size in differential diagnosis has been even more impressive. In an evaluation of the usefulness of the size, shape, and specific aortic contours for diagnosis of congenital heart disease, a review of the plain films of 610 cases of 12 commonly encountered lesions was carried out. The conclusions drawn were as follows: 1. The aorta is enlarged in patent ductus arteriosus, tetralogy of Fallot, tricuspid atresia without transposition, truncus arteriosus type IV, aortic stenosis, and coarctation. 2. The aorta is decreased in size in atrial septal defects, ventricular septal defects, anomalous pulmonary venous return, truncus arteriosus type I, II, and III, pulmonary stenosis, tricuspid atresia with transposition, transposition of the great vessels, and fibroelastosis. 3. In coarctation, patent ductus arteriosus, and aortic stenosis, the aortic configuration may be sufficiently characteristic to permit roentgen identification. 4. The aortic size and profile may differentiate patent ductus arteriosus from other left-to-right shunts. 5. The large aorta of tetralogy of Fallot distinguishes this condition from pulmonary stenosis with right-to-left interatrial shunt. 6. The large aorta is a useful sign in differentiating tricuspid atresia from tricuspid atresia with associated transposition of the great vessels. 7. Specific aortic contour is as reliable a diagnostic sign of coarctation of the aorta as is rib notching. This is of value because one sign may be present when the other is absent.

KITCHELL

Ormond, R. S., and Poznanski, A. K.: Pulmonary Veins in Rheumatic Heart Disease. Radiology 74: 542 (Apr.), 1960.

The posteroanterior films of 172 patients, who had undergone cardiac catheterization, were examined for the appearance of the pulmonary venous vasculature. All had valvular heart disease and the findings were not entirely in agreement with those of previous investigators. It was noted that pulmonary vein size was related to pressures within the left atrium, and an accurate estimate of the left atrial pressure could be obtained from plain posteroanterior films of the chest. The upper lobe veins were a more reliable index to elevated pressure than the lower lobe veins. However, both should be considered as well as the presence of Kerley's B lines, fluid, and distinctness of the veins. No appreciable

difference in appearance among valvular lesions producing an elevated pressure was observed.

KITCHELL

Schmitt, W., and Braun, H.: Kymographic Phase Analysis Studies and Heart Volume Determinations in Normotensive and Hypertensive Persons before and after Acute Decrease of Blood Pressure. Ztschr. Kreislaufforsch. **49**: 593 (July), 1960.

In 13 hypertensive and four normotensive persons 50 to 75 mg. of Penthonium caused decrease of venous pressure, increased circulation time, decrease of heart output (method of Broemser and Ranke) and decrease of heart size (determined by means of simultaneous roentgen tomography in 3 to 7 planes). The amplitude of contraction, determined by synchronous electrokymography of seven points, also decreased. In four of six patients with pathologic kymographic curves these became normal; this is attributed to decrease of an abnormally elevated residual ventricular blood volume.

LEPESCHKIN

S'jongers, J., and Enderle, J.: Detection of Anomalies of the Heart and the Intrathoracic Great Vessels in Natives of Ruanda. Acta cardiol. **15**: 140, 1960.

In the examination of 5,307 unselected chest microfilms of Negroes living in Ruanda (Central Africa), 4.45 per cent revealed pathologic anomalies of the heart and great vessels and 2.82 per cent were suggestive of abnormalities. A comparable investigation in the white Belgian population, living in Europe, revealed 13.53 per cent pathologic anomalies and 1.22 per cent suggestive abnormalities. Arteriosclerosis, chronic pulmonary heart disease, aneurysm of the aorta, and calcifications of the pericardium were more common in the white population. The Negroes showed often a globular-shaped heart. The frequency of chronic rheumatic heart disease and of congenital heart disease was the same in Belgium and in Ruanda.

BRACHFELD

Steinberg, I.: Localization of Bullets and Metallic Fragments in the Cardiovascular System: Role of Angiocardiography in 7 Cases. Am. J. Roentgenol. **83**: 998 (June), 1960.

Seven patients with metallic bodies in the cardiovascular system were studied angiocardiographically. Two of these patients had successful removal of bullets; one from the right ventricle, and the other from the right atrial appendage. Four patients were asymptomatic and were not subjected to surgery. The remaining patient, who had suffered a right hemiplegia and interventricular block after injury, had recurrent cerebrovascular seizures and, due to this, it was thought that the removal of a 38-caliber bullet from the posterior wall of the left ventricle would be too hazardous. This method of study will often indicate whether or not metallic fragments should be removed from the cardiovascular system. In other cases reassuring the patient of the unimportance of the fragments (which may not be causing trouble) will relieve the symptoms of a cardiac neurosis.

KITCHELL

Wang, C. C., and Reeves, J. D.: Mesenteric Vascular Disease. Am. J. Roentgenol. **83**: 895 (May), 1960.

The mesenteric arteries are subject to the same atheromatous, thrombotic, and embolic phenomena associated with the coronary and cerebral vessels. It has been said that mesenteric artery abnormalities exhibit roentgenographically a specific pattern. Although this belief is far from conclusive, there are certain roentgenographic manifestations encountered in mesenteric vascular occlusion that have not been adequately stressed. The present paper demonstrates and discusses some of these patterns observed in the past 10 years at the Massachusetts General Hospital. The clinical history is essential for interpretation of the roentgenographic findings, and in the presence of the following findings mesenteric vascular occlusion should be suspected: 1. Acute abdominal pain, vomiting, and shock in a patient presenting etiologic factors such as generalized atherosclerosis, atrial fibrillation, myocardial infarction, liver disease, blood dyscrasia, and antecedent aortic or abdominal surgery. Roentgenograms may show nonspecific ileus, signs of fixation of bowel loops with edema of intestinal walls and increase in intraperitoneal fluid. With contrast studies performed early, marked swelling of the mucosal folds with thickened bowel wall and occasionally an intraluminal pseudotumor formation may be noted. 2. In subacute and chronic cases abdominal pains may be anginal in nature and roentgenograms may be negative. Here contrast substances may outline narrowing of the bowel lumen simulating regional ileitis or ulcerative colitis, with or without evidence of malabsorption syndrome. Aortography may or may not demonstrate diminution of the mesenteric vascular flow. In our present state of knowledge, visualization of apparently patent mesenteric arteries does not exclude the diagnosis. If the mesenteric artery is well visualized, consideration should be given to the possibility of mesenteric venous thrombosis. The diagnosis

of mesenteric vascular disease is important because bowel and vascular surgery may offer the possibility of altering a grave prognosis.

KITCHELL

SURGERY AND CARDIOVASCULAR DISEASE

Björk, V. O.: An Effective Blood Heat Exchanger for Deep Hypothermia in Association with Extracorporeal Circulation but Excluding the Oxygenator. J. Thoracic Surg. **40**: 237 (Aug.), 1960.

The author describes a heat exchanger for deep hypothermia and enumerates the advantages of deep hypothermia with extracorporeal circulation without an oxygenator. These include: (1) less blood trauma and less hemolysis, (2) better oxygenation in the patient's lungs, (3) better protection for the myocardium than during other types of circulatory arrest, (4) easier operation, and (5) better blood volume control. In addition, cardiac arrest or complete circulatory arrest may be made at low temperature for longer intervals than with other methods. After 17 clinical cases, conclusions are that the ordinary pump-oxygenator (with the spinning disk oxygenator) is preferred at normal temperature in most cases, but combined with deep hypothermia in aortic valvular disease. Deep hypothermia is considered contraindicated in children because of the risk of brain damage, caused possibly by the aggregated thrombocytes and white blood corpuscles, which disappear from the circulation at a low temperature, returning to the circulation during rewarming, and occluding certain areas of the brain. In children, the myocardium is protected by local hypothermia. The heart may be surrounded with plastic bags of ice, after acetylcholine arrest, or isolated coronary perfusion with cold blood may be used.

MAXWELL

Blondeau, M., and Lenègre, J.: Conduction Disturbances Following Intracardiac Surgery. Arch. mal. coeur **53**: 740 (July), 1960.

Of 29 patients with aortic or pulmonary stenosis operated upon by closed heart methods, only two developed conduction disturbances. Of 28 patients with ostium secundum-type atrial septal defects operated upon by the open heart method, none developed them, while of 30 patients with ostium primum atrial, atrioventricular, or ventricular septal defects operated upon by this method, A-V block appeared in six and right bundle-branch block in 11. Of six patients with valvular pulmonary stenosis one developed patients with A-V block died. Histologic study peared in all nine patients with infundibular stenosis, A-V block appearing once. All cases of A-V block appeared during insertion of a prosthesis into a large septal defect; five of the seven patients with A-V block died. Histologic study showed that in these cases the common bundle or its bifucation was compressed by sutures. Right bundle-branch block did not seem to influence the prognosis. When it appeared, the initial portion of QRS was not modified; the wide R′ wave in V_1 always showed high voltage, even if no right ventricular hypertrophy pattern was present before appearance of the block. The duration of the QRS complex showed a continuous scatter between 0.08 and 0.17 second. Left bundle-branch block appeared only once, after operation for aortic stenosis.

LEPESCHKIN

Edwards, W. S.: Late Occlusion of Femoral and Popliteal Fabric Arterial Grafts. Surg., Gynec. & Obst. **110**: 714 (June), 1960.

An acute occlusion rate of 10 per cent and a 2-year occlusion rate of approximately 50 per cent were encountered in 125 patients having femoropopliteal bypass grafts of crimped Nylon or Teflon tubes. Direct inspection of the unsuccessful grafts and arteriographic study of patent ones in 22 patients indicated that the chief factor leading to thrombotic occlusion was the loss of elasticity and flexibility of the graft. Arteriograms during knee flexion frequently showed kinking and buckling of a graft that was reasonably straight while the leg was extended. Experiments were cited to show that loss of flexibility was a result of fibrosis of the graft, the degree of which reached a maximum within 6 months. Two infrequent causes of graft failure were local infection and progressive arteriosclerotic obstruction proximally or distally. The author presently prefers endarterectomy for relief of short-segment femoropopliteal obstruction and reserves grafting for long-segment obstructions.

ROGERS

NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, New York
Telephone Gramercy 7-9170

J. SCOTT BUTTERWORTH, M.D.

J. Scott Butterworth, M.D., the new President of the American Heart Association, is an eminent clinician and authority on the development of audio-visual instruments and aids for teaching cardiology.

Dr. Butterworth is Associate Professor of Medicine, New York University School of Medicine. He is also Attending Physician at University Hospital, Visiting Physician at Bellevue Hospital, and Consulting Cardiologist at five other hospitals in the New York metropolitan area.

Over the years, he has been a member and chairman of many Heart Association councils and major committees, especially those concerned with professional and public education. His AHA activities date back to 1950 when he served a two-year term on its national Board. He has since been Chairman of the Association's Professional Education Committee and of its Publications Committee. He has served on the Editorial Board of *Circulation*, has been a Vice President of the national organization since 1959, and has served on the Board of the New York Heart Association since 1950.

Born in Iowa City, Iowa, Dr. Butterworth's family moved to Ithaca, New York, where he attended Cornell University, receiving an A.B. degree in 1932, an M.S. in chemistry in 1933, and an M.D. degree in 1937. In 1942, he obtained a Doctor of Medical Science degree from Columbia University.

Following his internship at New York Post-Graduate Medical School and Hospital in 1937-38, he was a Melville Fellow in Cardiology from 1939-41.

Dr. Butterworth was awarded the Billings Gold Medal of the American Medical Association in 1953 and the Award of Merit of the American Heart Association in 1959. He is a member of Sigma Xi, the American Federation for Clinical Research, a Fellow of the American College of Physicians and a diplomate of the American Board of Internal Medicine and the subspecialty board of Cardiovascular Diseases.

Dr. Warren Chosen as President-Elect; New AHA Officers Elected for 1961-62

James V. Warren, M.D., Professor and Chairman of the Department of Medicine, Ohio State University, Columbus, was named President-elect of the American Heart Association and J. Scott Butterworth, M.D., was installed as President for the 1961-62 term at the Association's Annual Meeting in Bal Harbour, Florida.

Retiring President Oglesby Paul, M.D., Clinical Associate Professor of Medicine, Uni-

versity of Illinois College of Medicine, Chicago, became Chairman of the Heart Association's Central Committee for Medical and Community Program.

In addition to choosing a President-elect, the AHA Assembly named nine Vice Presidents, a Treasurer and 19 members to the Board of Directors.

Newly-elected as Vice Presidents were William W. L. Glenn, M.D., New Haven; Judge Dulany Foster, Baltimore; C. Victor Johnson, New York; John G. Smith, M.D., Rocky Mount, North Carolina. Re-elected as Vice Presidents were Brig. Gen. Philip P. Ardery, Louisville; John D. Brundage, Montclair, New Jersey; Charles H. Rammelkamp, Jr., M.D., Cleveland; Merritt H. Stiles, M.D., Spokane; and Helen B. Taussig, M.D., Baltimore.

1962 Subscription Renewals

Subscriptions for *Circulation* and *Circulation Research*, official scientific publications of the American Heart Association, may now be renewed for 1962 through the Subscription Department, American Heart Association, 44 East 23rd Street, New York 10, New York.

The new subscription rate for *Circulation Research*, which becomes a monthly instead of a bi-monthly in January, 1962, is $14 a year ($15 foreign). In combination with a subscription to *Circulation* the rate is $25 ($28 foreign). A special rate of $9 annually for *Circulation Research* is available in the U. S. only for medical students, interns, residents and research fellows.

The rate for *Circulation* remains unchanged at $14 yearly ($15 foreign). A special rate of $9 is available for medical students, interns and residents in the U.S. only.

Fourth World Cardiology Congress Maps Program of Varied Interest

The Organizing Committee for the Fourth World Congress of Cardiology is planning to have at least 275 original scientific papers presented at the sessions from October 7-13, 1962, in Mexico City.

Of this number, it is anticipated that approximately 260 papers will be by individual investigators or small research groups. The remainder are to be based on results obtained by a laboratory, clinic or institution. The program will also include symposia, panels and informal conferences through which specialists may develop various aspects of a given subject in their particular fields.

To assure the maximum presentation of a variety of papers and the widest possible participation by those attending, methods are being devised by the Organizing Committee for abridged presentations of some papers.

Subjects officially approved for discussion in papers from institutions, and at symposia, panels and conferences, are:

Biochemistry of heart failure; Electrolytes in the cardiac patient; Diagnostic value of dye dilution curves; Aldosteronism and arterial hypertension; Inhibitors of monoaminoxidase; Fibrinolysis and coagulation; Intracardiac conduction disturbances; Basic advances in experimental electrocardiography; A-V block and artificial pacemakers; Phonocardiography and its contributions to hemodynamics; Anatomy and etiology of congenital heart disease; Selective angiocardiography; Late advances on pulmonary circulation.

Also, Cardiopathies in diseases of the connective tissue; Space medicine in the cardiovascular field; Stress in cardiovascular diseases; Cerebral anoxia in the cardiac patient; Intracavitary cardiac surgery; Neurological complications in cardiovascular surgery; Long-term results of mitral commissurotomy; Cardiac resuscitation; New aspects of cardiac arrhythmias; Cholesterol and atherosclerosis; Recent advances in arterial hypertension; Diagnostic pitfalls in myocardial infarction; Myocarditis of uncertain origin; New physiognomy of bacterial endocarditis; and Diagnosis of cardiac tumors.

Further information regarding the Congress may be obtained from Dr. I. Costero, Secretary General, Instituto Nacional de Cardiologia, Ave. Cuauhtemoc 300, Mexico 7, D.F.

Meetings Calendar

January 22-24: Inter-American Conference on Congenital Defects, Los Angeles. S. E. Henwood, International Medical Congress, Ltd., 120 Broadway, New York City.

January 29-February 1: American College of Surgeons, Sectional Meeting, Los Angeles. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

February 3-6: Congress on Medical Education and Licensure, Chicago. W. S. Wiggins, 535 N. Dearborn, Chicago 10, Illinois.

February 7-10: American College of Radiology, New York. W. C. Stronach, 20 No. Wacker Dr., Chicago 6, Illinois.

February 8-10: Society of University Surgeons, Cleveland. C. F. Kittle, University of Kansas Medical Center, Kansas City 12, Kansas.

March 5-7: American College of Surgeons, Sectional Meeting, Detroit. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

March 26-28: American College of Surgeons, Sectional Meeting, Memphis. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

March 30-April 1: American Psychosomatic Society, Annual Meeting, Rochester, New York. Stewart Wolf, 265 Nassau Rd., Roosevelt, New York.

April 2-4: American Radium Society, New York. C. G. Stetson, 35 Engle St., Englewood, New Jersey.

April 6-8: American Society of Internal Medicine, Philadelphia. G. T. Bates, 350 Post St., San Francisco 8, California.

April 6-13: American Academy of General Practice, Las Vegas, Nevada. Mac F. Cahal, Volker at Brookside, Kansas City 12, Missouri.

April 9-13: American College of Physicians, Philadelphia. E. C. Rosenow, Jr., 4200 Pine St., Philadelphia 4, Pennsylvania.

April 13-14: American Society for Artificial Internal Organs, Atlantic City. E. C. Peirce II, 514 W. Church Ave., Knoxville 1, Tennessee.

April 16-18: American College of Surgeons, Sectional Meeting, Washington, D.C. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

April 29: American Federation for Clinical Research, Atlantic City. J. E. Bryan, 250 W. 57th St., New York 19, New York.

May 1-2: Association of American Physicians (members only), Atlantic City. Eugene A. Stead, Jr., Duke Hospital, Durham, North Carolina.

May 29-June 2: American College of Cardiology, Denver. Philip Reichert, Empire State Bldg., New York 1, New York.

June 23: International Cardiovascular Society, North American Chapter, Chicago. R. A. Deterling, Jr., 171 Harrison Ave., Boston 11, Massachusetts.

June 25-29: American Medical Association, Annual Meeting, Chicago. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

Abroad

September 5-8: International Congress of Internal Medicine, Munich. Prof. E. Welheim, Luitpeldkrankenhaus, Wurzburg, Germany.

October 7-13: Fourth World Congress of Cardiology, Mexico City. I. Costero, Secretary General, Ave. Cuauhtemoc 300, Mexico 7, D.F.

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